```
=> d his l18-

     FILE 'HCAPLUS' ENTERED AT 15:47:58 ON 08 JAN 2003
                  E BEMIS GUY/AU
L18           39 S E3-5
                  E GOLEC JULIAN/AU
L19           44 S E3-5
                  E LAUFFER DAVID/AU
L20           31 S E3-5
                  E MULLICAN MICHAEL/AU
L21           53 S E3-5
                  E MURCKO MARK/AU
                  E MURCKO MARK/AU
L22           94 S E2-5
                  E LIVINGSTON DAVID/AU
L23           74 S E3,E6-7
L24            5 S L18 AND L19 AND L20 AND L21 AND L22 AND L23
                  SELECT RN L24 4

     FILE 'REGISTRY' ENTERED AT 15:54:13 ON 08 JAN 2003
L25          904 S E1-904

     FILE 'HCAPLUS' ENTERED AT 15:56:06 ON 08 JAN 2003
L26            5 S L24 AND L25 Inventor's work - voluminous so I didn't print
                  it, but will do if you'd like to have it.
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L28            0 S L27
L29               STR L27
L30            0 S L29
L31               STR L27
L32            0 S L31
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L34            5 S L33
L35           35 S L33 FULL  35 compds from L33

     FILE 'HCAPLUS' ENTERED AT 16:12:06 ON 08 JAN 2003
L36            7 S L35  7 cits from L35. d que stat is attached.
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=> d que stat l36
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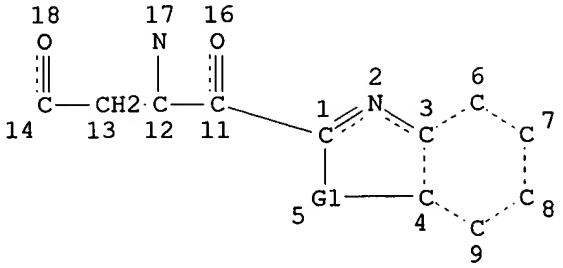


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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

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RING(S) ARE ISOLATED OR EMBEDDED
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STEREO ATTRIBUTES: NONE
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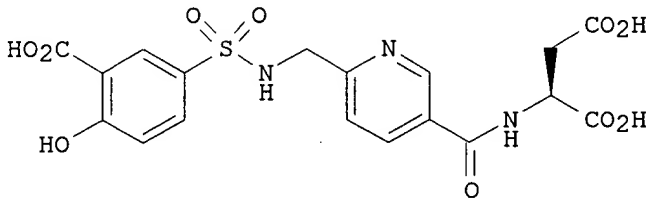
L36 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:782787 HCAPLUS
DOCUMENT NUMBER: 138:98
TITLE: Identification of potent and selective small-molecule inhibitors of caspase-3 through the use of extended tethering and structure-based drug design
AUTHOR(S): Choong, Ingrid C.; Lew, Willard; Lee, Dennis; Pham, Phuongly; Burdett, Matthew T.; Lam, Joni W.; Wiesmann, Christian; Luong, Tinh N.; Fahr, Bruce; DeLano, Warren L.; McDowell, Robert S.; Allen, Darin A.; Erlanson, Daniel A.; Gordon, Eric M.; O'Brien, Tom
CORPORATE SOURCE: Sunesis Pharmaceuticals Inc., South San Francisco, CA, 94080, USA
SOURCE: Journal of Medicinal Chemistry (2002), 45(23), 5005-5022
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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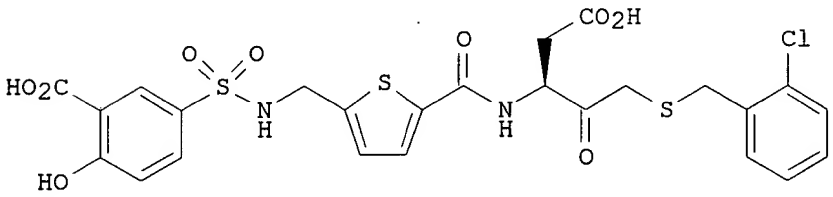


II

AB The design, synthesis, and in vitro activities of a series of potent and selective small-mol. inhibitors of caspase-3 are described. From extended tethering, a salicylic acid fragment was identified as having binding affinity for the S4 pocket of caspase-3. X-ray crystallog. and mol. modeling of the initial tethering hit resulted in the synthesis of (I), which reversibly inhibited caspase-3 with a Ki = 40 nM. Further optimization led to the identification of a series of potent and selective inhibitors with Ki values in the 20-50 nM range. One of the most potent compds. in this series, (II), inhibited caspase-3 with a Ki = 20 nM and selectivity of 8-500-fold for caspase-3 vs a panel of seven caspases (1, 2, and 4-8). A high-resoln. X-ray cocrystal structure of I and II supports the predicted binding modes of our compds. with caspase-3.

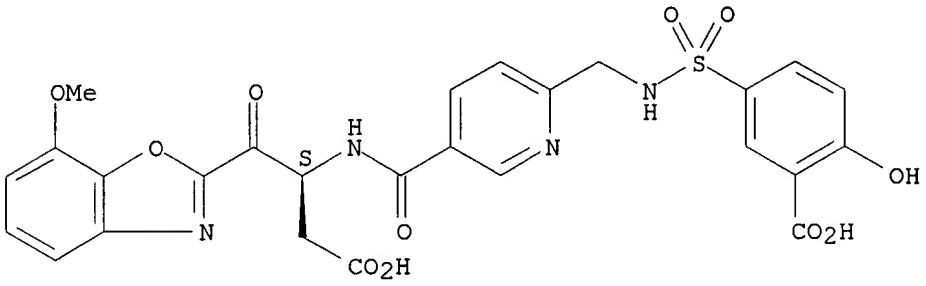
IT **476363-06-1P 476363-32-3P**
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(identification of potent and selective small-mol. inhibitors of caspase-3 through the use of extended tethering and structure-based drug design)

RN 476363-06-1 HCAPLUS

CN 2-Benzoxazolebutanoic acid, .beta.-[[[6-[[[(3-carboxy-4-hydroxyphenyl)sulfonyl]amino]methyl]-3-pyridinyl]carbonyl]amino]-7-methoxy-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

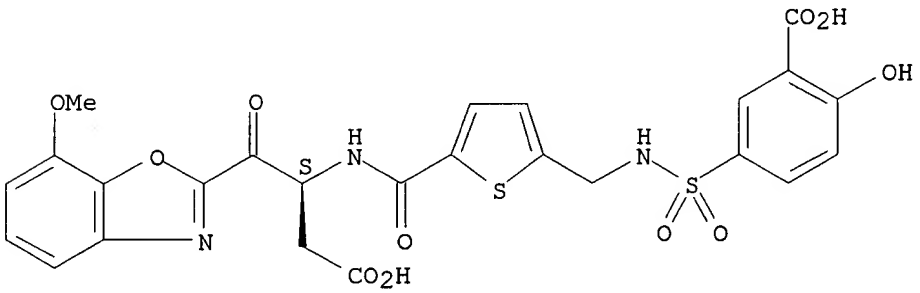
Absolute stereochemistry.



RN 476363-32-3 HCAPLUS

CN 2-Benzoxazolebutanoic acid, .beta.-[[[5-[[[(3-carboxy-4-hydroxyphenyl)sulfonyl]amino]methyl]-2-thienyl]carbonyl]amino]-7-methoxy-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:136764 HCAPLUS

DOCUMENT NUMBER: 130:196957

TITLE: Preparation of bicyclic peptide derivatives as interleukin-1.beta. converting enzyme inhibitors

INVENTOR(S): Batchelor, Mark James; Bebbington, David; Bemis, Guy w.; Fridman, Wolf Herman; Gillespie, Roger John; Golec, Julian M. C.; Lauffer, David J.; Livingston, David J.; Matharu, Saroop Singh; Mullican, Michael D.; Murcko, Mark A.; Murdoch, Robert; Zelle, Robert E.

PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA

SOURCE: U.S., 189 pp., Cont.-in-part of U.S. Ser. No. 575,641. CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5874424 | A | 19990223 | US 1996-598332 | 19960208 |
| US 6008217 | A | 19991228 | US 1995-575641 | 19951220 |
| US 6204261 | B1 | 20010320 | US 1996-761483 | 19961206 |
| WO 9722619 | A2 | 19970626 | WO 1996-US20843 | 19961220 |
| WO 9722619 | A3 | 19971016 | | |
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| ZA 9610798 | A | 19970707 | ZA 1996-10798 | 19961220 |
| AU 9715222 | A1 | 19970714 | AU 1997-15222 | 19961220 |
| AU 735075 | B2 | 20010628 | | |
| EP 869967 | A2 | 19981014 | EP 1996-945318 | 19961220 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 9612258 | A | 19990713 | BR 1996-12258 | 19961220 |
| CN 1229412 | A | 19990922 | CN 1996-199828 | 19961220 |
| JP 2002507961 | T2 | 20020312 | JP 1997-523098 | 19961220 |
| NO 9802597 | A | 19980812 | NO 1998-2597 | 19980605 |
| US 6258948 | B1 | 20010710 | US 1999-400639 | 19990921 |
| US 6423840 | B1 | 20020723 | US 2001-773477 | 20010131 |

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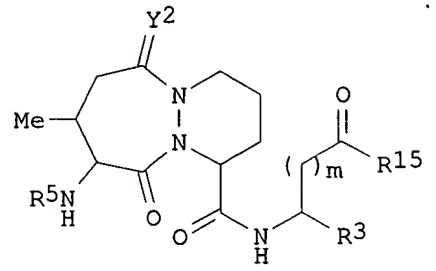
| PRIORITY APPLN. INFO.: | US 1995-575641 | A2 | 19951220 | |
| | US 1996-598332 | A2 | 19960208 | |
| | US 1996-712878 | A2 | 19960912 | |
| | US 1996-31495P | P | 19961126 | |
| | US 1996-761483 | A | 19961206 | |
| | WO 1996-US20843 | W | 19961220 | |

OTHER SOURCE(S): MARPAT 130:196957
GI



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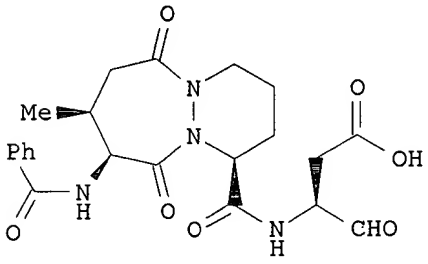


II

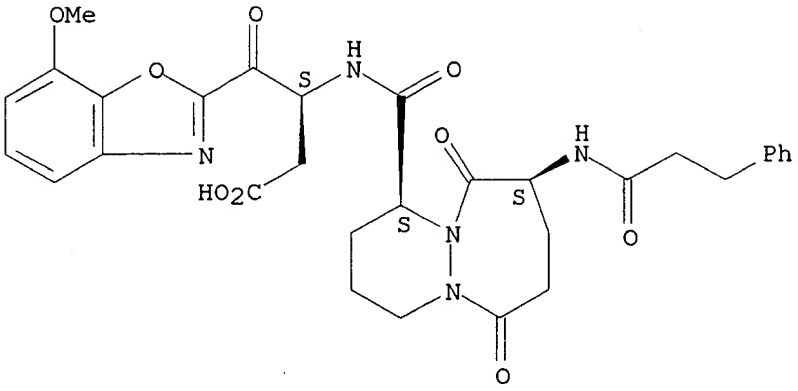
AB Title compds. I [m = 1-2; R3 = CN, CHO, COCH2-T1-R11, COCH2F, C:NOR9, COAr2; R5 = COR10, CO2R9, CONR102, SO2R9, SO2NHR10, COCH2OR9, COCOR10, R9, H, COCO2R10, COCONR9R10; Y = O, H2; T1 = O, S, S(O), SO2; R9 = Ar3, (un)branched C1-6 alkyl optionally unsatd. and optionally substituted with Ar3; R10 = H, Ar3, C3-6 cycloalkyl, any group R9; R11 = Ar4, (CH2)1-3Ar4, H, COAr4; R15 = OH, OAr3, NHOH, (un)branched C1-6 alkoxy optionally unsatd. and optionally substituted with Ar3, CONH2, OR5, OH, OR9, CO2H; Ar2 = (un)substituted 2-oxazolyl, 2-benzoxazolyl, 2-thiazolyl, 2-benzothiazolyl; Ar3, Ar4 = optionally substituted, nitrogen-contg. heteroarom. or heterocyclic group contg. 1-3 rings] were prepd. as inhibitors of interleukin-1.beta. converting enzyme. Thus, bicyclic peptide deriv. II was prepd. and shown to have Ki = 13 nM in a UV-visible assay and IC50 = 11000 nM in a peripheral blood mononuclear cell (PBMC) assay.

IT **175209-35-5P 175209-36-6P 175209-84-4P**
**192753-37-0P 192753-38-1P 192754-56-6P**
**192754-57-7P 192758-04-6P 192758-50-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of bicyclic peptide derivs. as interleukin-1.beta. converting enzyme inhibitors)

RN 175209-35-5 HCAPLUS

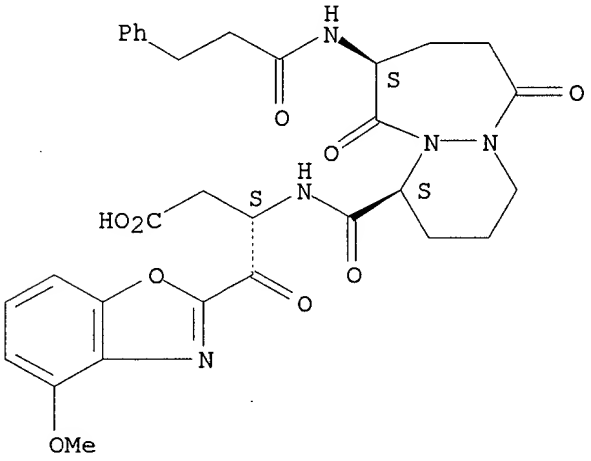
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.beta.-[[[(1S,9S)-octahydro-6,10-dioxo-9-[(1-oxo-3-phenylpropyl)amino]-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



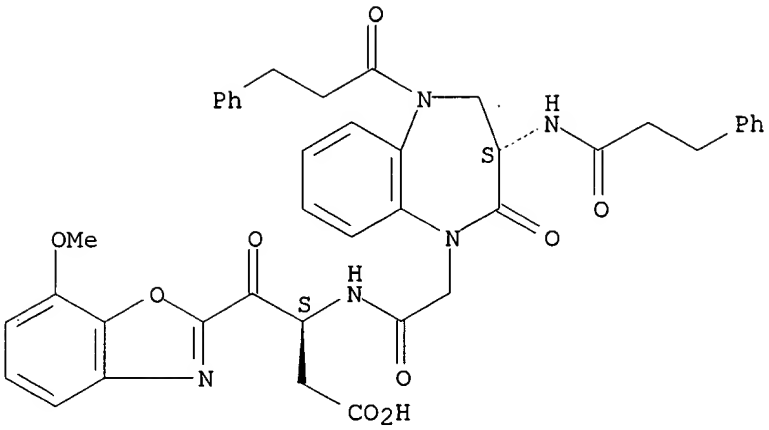
RN 175209-36-6 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 4-methoxy-.beta.-[[[(1S,9S)-octahydro-6,10-dioxo-9-[(1-oxo-3-phenylpropyl)amino]-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



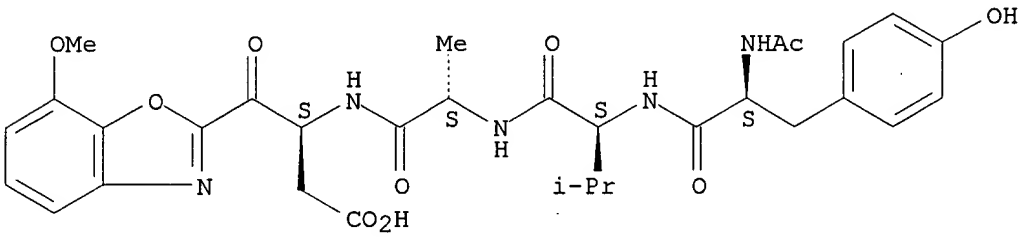
RN 175209-84-4 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[[(3S)-2,3,4,5-tetrahydro-2-oxo-5-(1-oxo-3-phenylpropyl)-3-[(1-oxo-3-phenylpropyl)amino]-1H-1,5-benzodiazepin-1-yl]acetyl]amino]-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



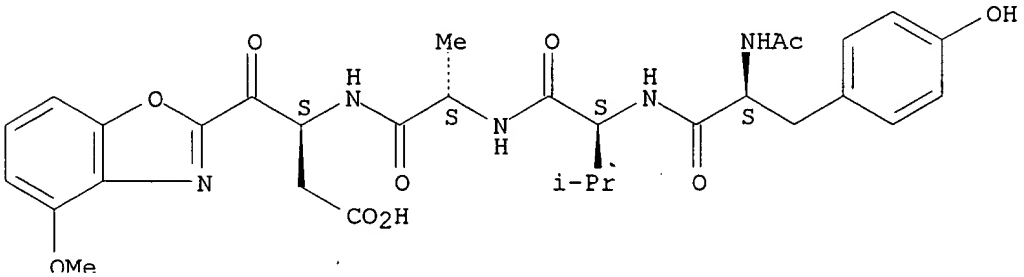
RN 192753-37-0 HCAPLUS
CN L-Alaninamide, N-acetyl-L-tyrosyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(7-methoxy-2-benzoxazolyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



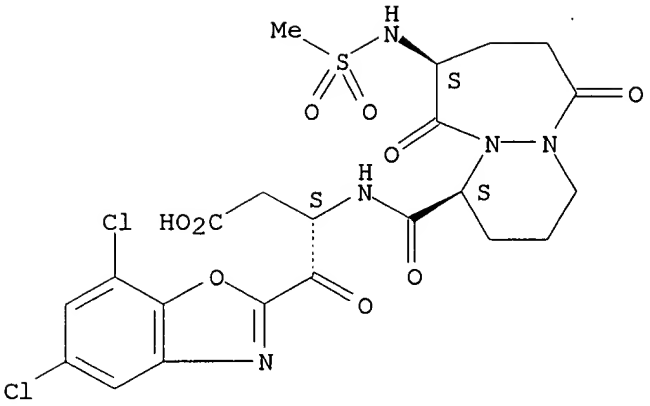
RN 192753-38-1 HCAPLUS
CN L-Alaninamide, N-acetyl-L-tyrosyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(4-methoxy-2-benzoxazolyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



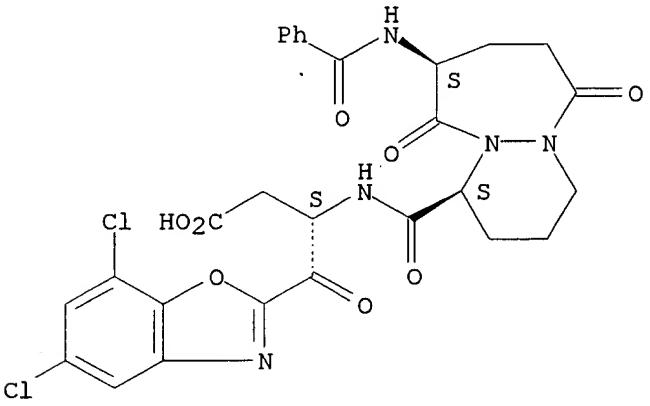
RN 192754-56-6 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 5,7-dichloro-.beta.-[[[(1S,9S)-octahydro-9-[(methylsulfonyl)amino]-6,10-dioxo-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 192754-57-7 HCAPLUS
CN 2-Benzoxazolebutanoic acid, .beta.-[[[(1S,9S)-9-(benzoylamino)octahydro-6,10-dioxo-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-5,7-dichloro-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 192758-04-6 HCAPLUS
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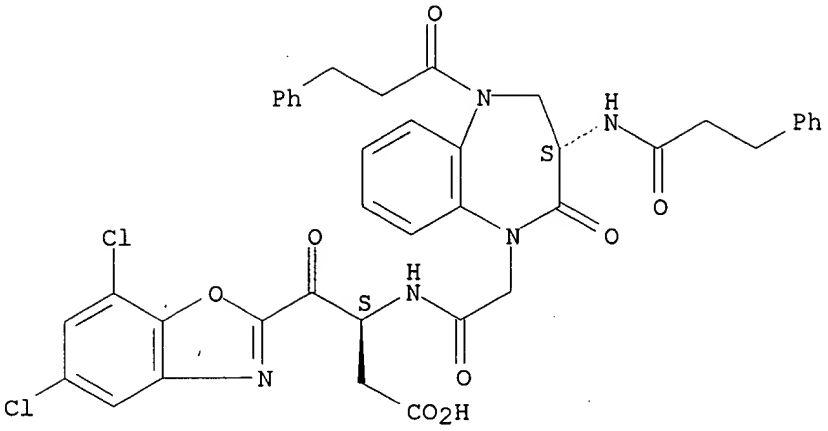
Absolute stereochemistry.



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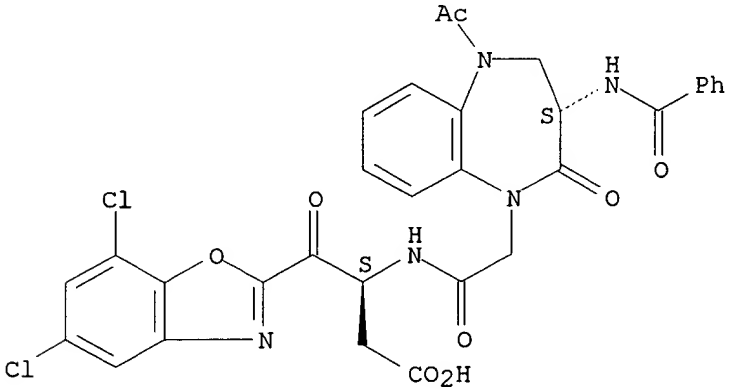
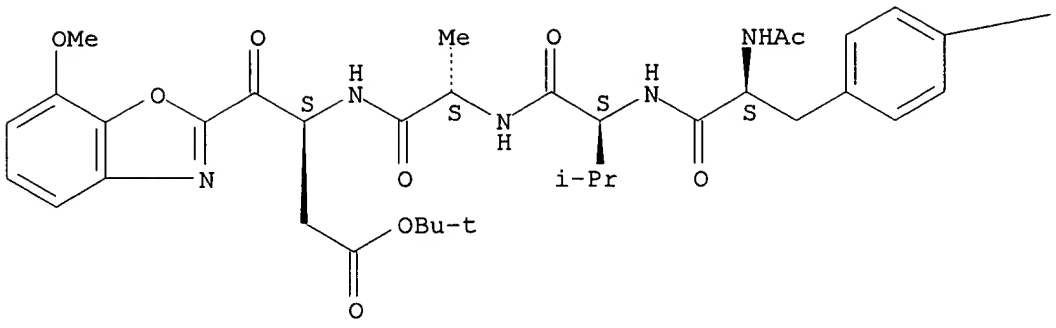
Absolute stereochemistry.



IT **175211-18-4P 175211-19-5P 192753-85-8P**
**192753-87-0P 192755-85-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of bicyclic peptide derivs. as interleukin-1.beta. converting enzyme inhibitors)
RN 175211-18-4 HCAPLUS
CN L-Alaninamide, N-acetyl-O-(1,1-dimethylethyl)-L-tyrosyl-L-valyl-N-[(1S)-3-(1,1-dimethylethoxy)-1-[(7-methoxy-2-benzoxazolyl)carbonyl]-3-oxopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



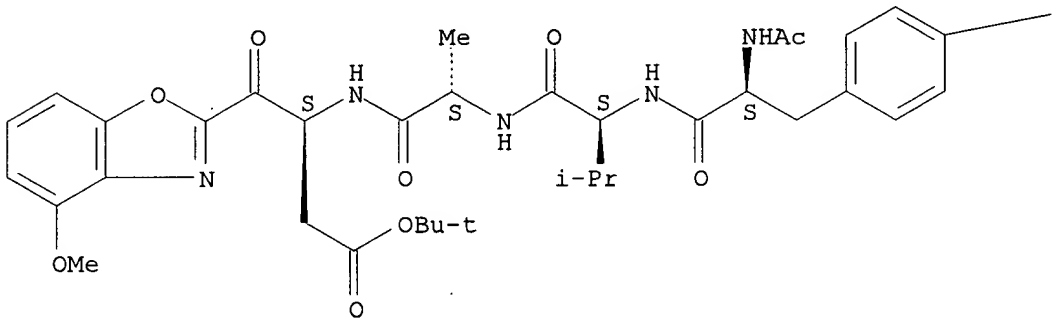
PAGE 1-B

—OBu-t

RN 175211-19-5 HCAPLUS
CN L-Alaninamide, N-acetyl-O-(1,1-dimethylethyl)-L-tyrosyl-L-valyl-N-[(1S)-3-(1,1-dimethylethoxy)-1-[(4-methoxy-2-benzoxazolyl)carbonyl]-3-oxopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

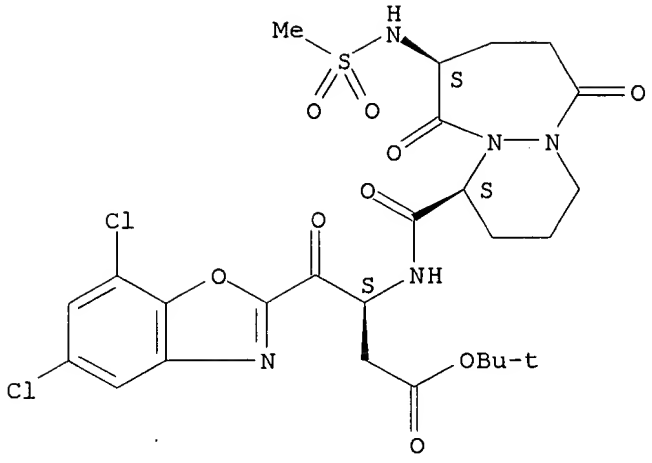


PAGE 1-B

—OBu-t

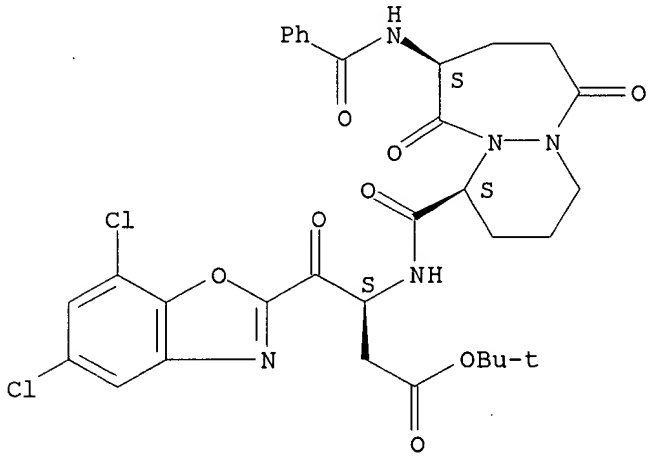
RN 192753-85-8 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 5,7-dichloro-.beta.-[[[(1S,9S)-octahydro-9-[(methylsulfonyl)amino]-6,10-dioxo-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-.gamma.-oxo-, 1,1-dimethylethyl ester, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 192753-87-0 HCAPLUS
CN 2-Benzoxazolebutanoic acid, .beta.-[[[(1S,9S)-9-(benzoylamino)octahydro-6,10-dioxo-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-5,7-dichloro-.gamma.-oxo-, 1,1-dimethylethyl ester, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



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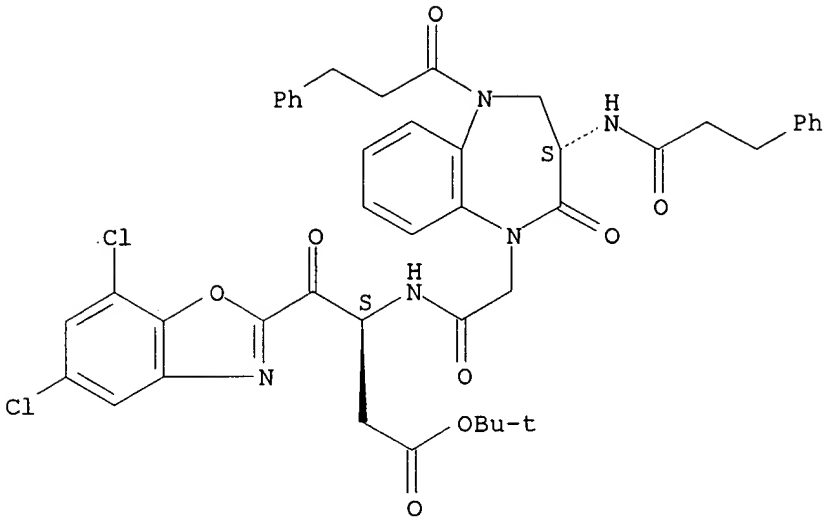
CN 2-Benzoxazolebutanoic acid, 5,7-dichloro-.gamma.-oxo-.beta.-[[[(3S)-2,3,4,5-tetrahydro-2-oxo-5-(1-oxo-3-phenylpropyl)-3-[(1-oxo-3-phenylpropyl)amino]-1H-1,5-benzodiazepin-1-yl]acetyl]amino]-, 1,1-dimethylethyl ester, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:788773 HCAPLUS
DOCUMENT NUMBER: 130:66805
TITLE: Preparation of peptide inhibitors of interleukin-1.beta. converting enzyme
INVENTOR(S): Bemis, Guy W.; Golec, Julian M. C.; Lauffer, David J.; Mullican, Michael D.; Murcko, Mark A.; Livingston, David J.
PATENT ASSIGNEE(S): Vertex Pharmaceuticals, Incorporated, USA
SOURCE: U.S., 106 pp., Cont.-in-part of U.S. 5,656,627. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5847135 | A | 19981208 | US 1995-440898 | 19950525 |
| US 5756466 | A | 19980526 | US 1994-261452 | 19940617 |
| US 5656627 | A | 19970812 | US 1995-405581 | 19950317 |
| US 5716929 | A | 19980210 | US 1995-464964 | 19950605 |
| US 6103711 | A | 20000815 | US 1995-465216 | 19950605 |
| CA 2192089 | AA | 19951228 | CA 1995-2192089 | 19950616 |
| WO 9535308 | A1 | 19951228 | WO 1995-US7617 | 19950616 |
| W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT | | | | |
| RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9529446 | A1 | 19960115 | AU 1995-29446 | 19950616 |
| AU 709114 | B2 | 19990819 | | |

| | | | | | |
|---|---|---|---|---|---|
| EP 784628 | A1 | 19970723 | EP 1995-925257 | 19950616 | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | | |
| CN 1159196 | A | 19970910 | CN 1995-194381 | 19950616 | |
| BR 9508051 | A | 19971021 | BR 1995-8051 | 19950616 | |
| HU 76622 | A2 | 19971028 | HU 1996-3475 | 19950616 | |
| JP 10504285 | T2 | 19980428 | JP 1996-502478 | 19950616 | |
| NO 9605365 | A | 19970217 | NO 1996-5365 | 19961213 | |
| FI 9605036 | A | 19970214 | FI 1996-5036 | 19961216 | |
| US 5973111 | A | 19991026 | US 1997-828941 | 19970328 | |
| US 6420522 | B1 | 20020716 | US 1999-430822 | 19991029 | |
| US 2002099042 | A1 | 20020725 | US 2001-886773 | 20010621 | |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1994-261452 | A2 | 19940617 |
| US 1995-405581 | A2 | 19950317 |
| US 1995-440898 | A3 | 19950525 |
| US 1995-465216 | A3 | 19950605 |
| WO 1995-US7617 | W | 19950616 |
| US 1999-430822 | A3 | 19991029 |

OTHER SOURCE(S): MARPAT 130:66805

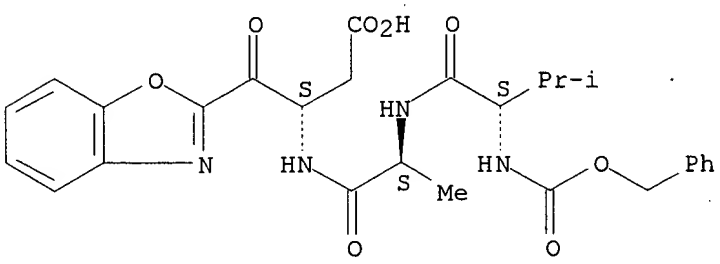
AB Interleukin-1.beta. converting enzyme inhibitors R1NHX1[(CH2)mT](CH2)gR3 (X1 = CH, N; g = 0, 1; m = 0-2; T = a cyclic group, OH, CF3, COCO2H, CO2H; R1 = R4ZNR5CR6R7CO or substituted derivs., where R4 represents certain ring systems; R5 = H, a cyclic group, alkyl, arylcarbonyl, arylsulfonyl, etc.; CR6R7 form a satd. carbocyclic or heterocyclic ring; R3 = CN, 1-alkenyl, alkoxyiminomethyl) were prepd. Thus, N-(N-acetyltyrosinylvalinylpipecolyl)-3-amino-4-oxobutanoic acid was prepd. and showed IC50 = 6-11 .mu.M for inhibition of interleukin-1.beta. converting enzyme.

IT **175209-23-1P 175209-31-1P 175209-32-2P**
**175209-35-5P 175209-36-6P 175209-50-4P**
**175209-69-5P 175209-70-8P 175209-78-6P**
**175209-84-4P 192753-37-0P 192753-38-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of peptide inhibitors of interleukin-1.beta. converting enzyme)

RN 175209-23-1 HCAPLUS

CN L-Alaninamide, N-[(phenylmethoxy)carbonyl]-L-valyl-N-[(1S)-2-(2-benzoxazolyl)-1-(carboxymethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

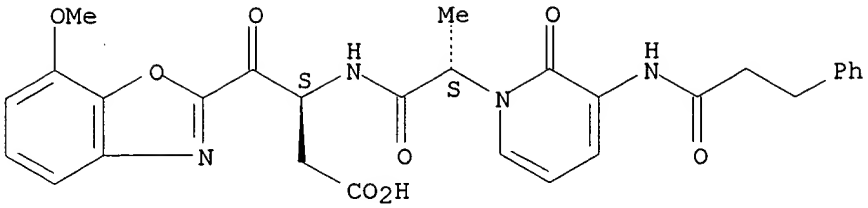
Absolute stereochemistry. Rotation (-).




RN 175209-31-1 HCAPLUS

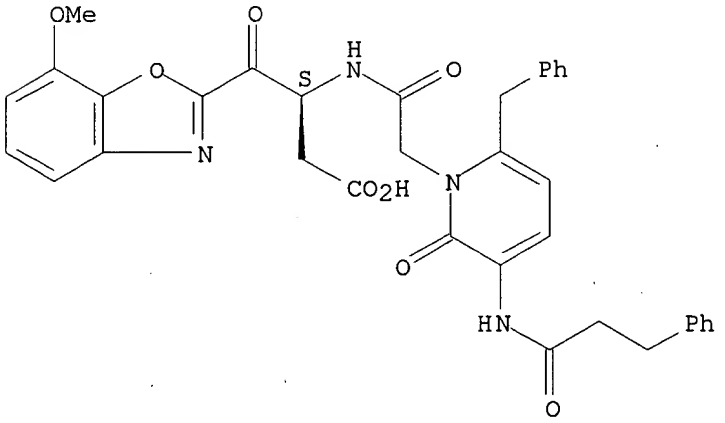
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[(2S)-1-oxo-2-[2-oxo-3-[(1-oxo-3-phenylpropyl)amino]-1(2H)-pyridinyl]propyl]amino]-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



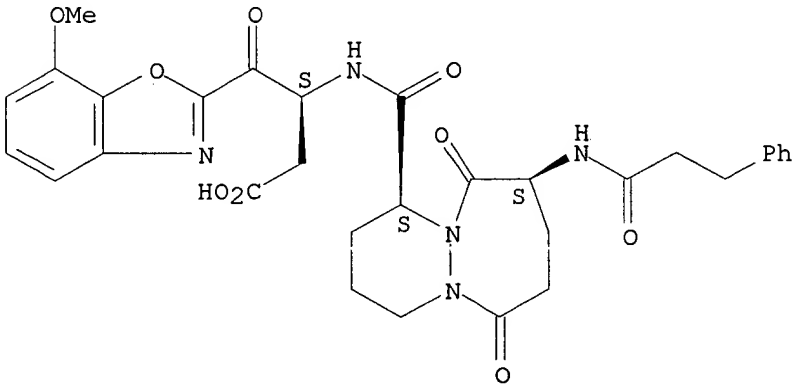
RN 175209-32-2 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[[2-oxo-3-[(1-oxo-3-phenylpropyl)amino]-6-(phenylmethyl)-1(2H)-pyridinyl]acetyl]amino]-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 175209-35-5 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.beta.-[[[(1S,9S)-octahydro-6,10-dioxo-9-[(1-oxo-3-phenylpropyl)amino]-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

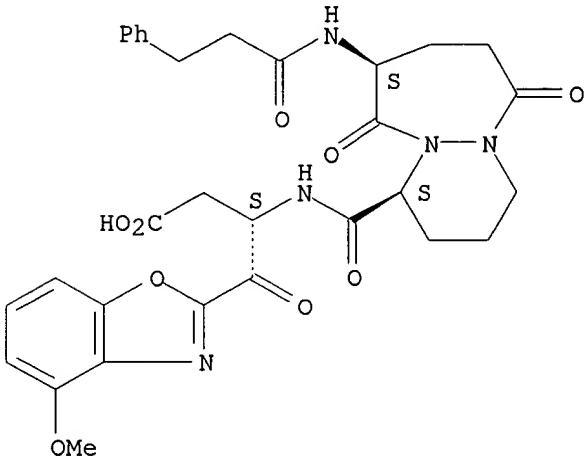
Absolute stereochemistry.



RN 175209-36-6 HCAPLUS

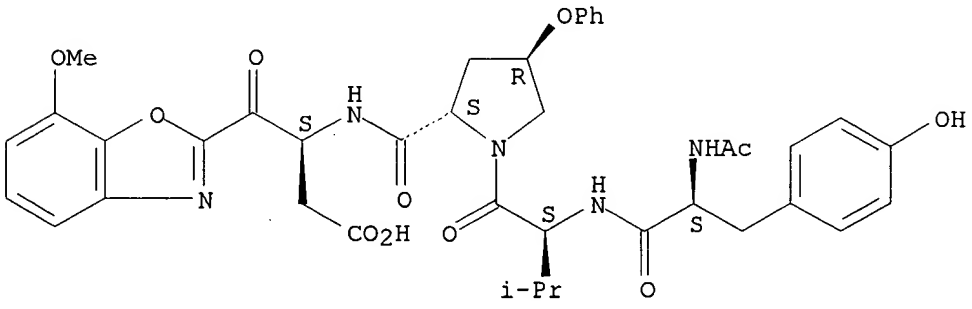
CN 2-Benzoxazolebutanoic acid, 4-methoxy-.beta.-[[[(1S,9S)-octahydro-6,10-dioxo-9-[(1-oxo-3-phenylpropyl)amino]-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



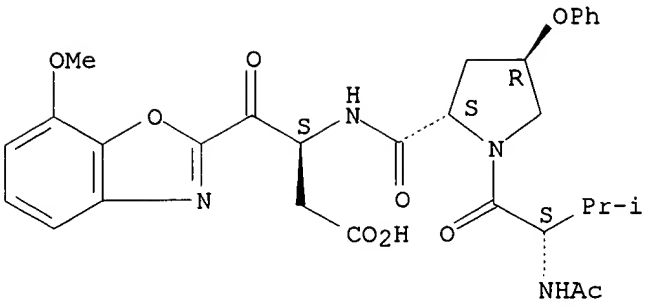
RN 175209-50-4 HCAPLUS
CN L-Prolinamide, N-acetyl-L-tyrosyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(7-methoxy-2-benzoxazolyl)-2-oxoethyl]-4-phenoxy-, (4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



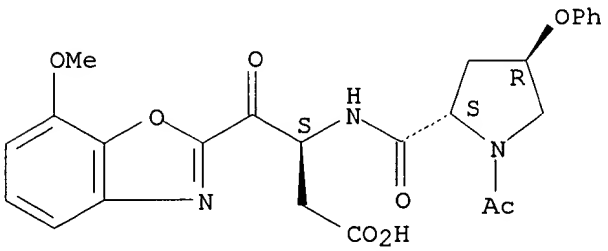
RN 175209-69-5 HCAPLUS
CN L-Prolinamide, N-acetyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(7-methoxy-2-benzoxazolyl)-2-oxoethyl]-4-phenoxy-, (4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



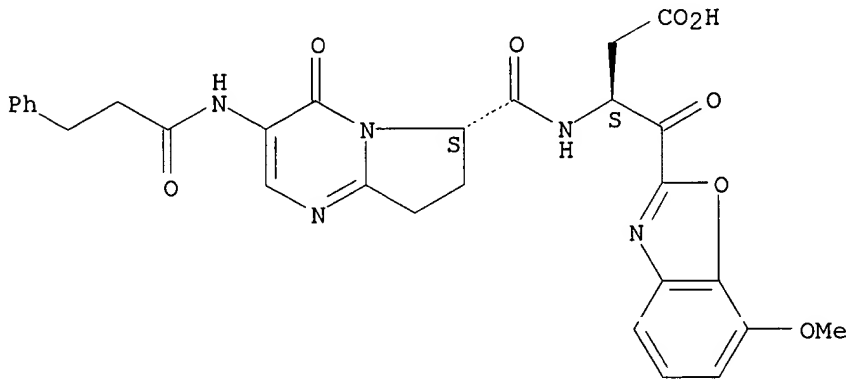
RN 175209-70-8 HCAPLUS
CN 2-Benzoxazolebutanoic acid, .beta.-[[[(2S,4R)-1-acetyl-4-phenoxy-2-pyrrolidinyl]carbonyl]amino]-7-methoxy-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 175209-78-6 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[[(6S)-4,6,7,8-tetrahydro-4-oxo-3-[(1-oxo-3-phenylpropyl)amino]pyrrolo[1,2-a]pyrimidin-6-yl]carbonyl]amino]-, (.beta.S)- (9CI) (CA INDEX NAME)

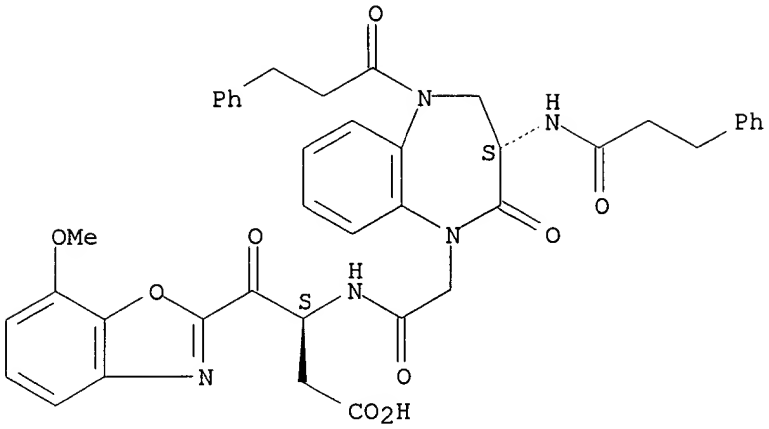
Absolute stereochemistry.



RN 175209-84-4 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[[(3S)-2,3,4,5-tetrahydro-2-oxo-5-(1-oxo-3-phenylpropyl)-3-[(1-oxo-3-phenylpropyl)amino]-1H-1,5-benzodiazepin-1-yl]acetyl]amino]-, (.beta.S)- (9CI) (CA INDEX

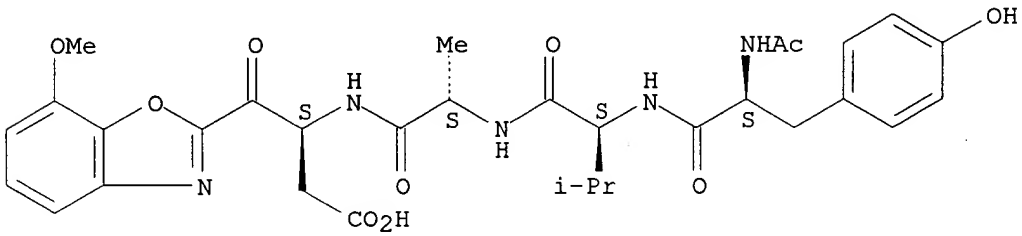
NAME)

Absolute stereochemistry.



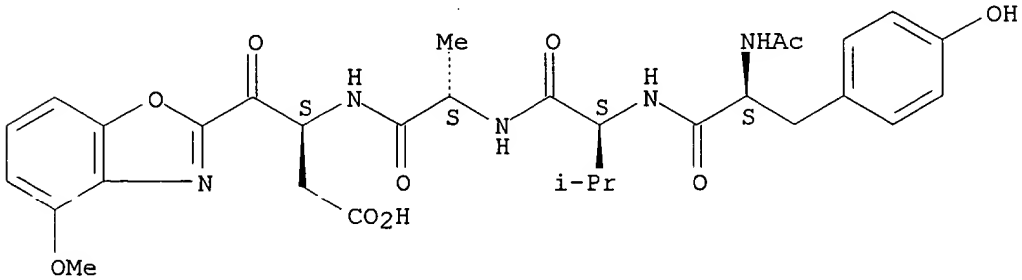
RN 192753-37-0 HCAPLUS
CN L-Alaninamide, N-acetyl-L-tyrosyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(7-methoxy-2-benzoxazolyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 192753-38-1 HCAPLUS
CN L-Alaninamide, N-acetyl-L-tyrosyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(4-methoxy-2-benzoxazolyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

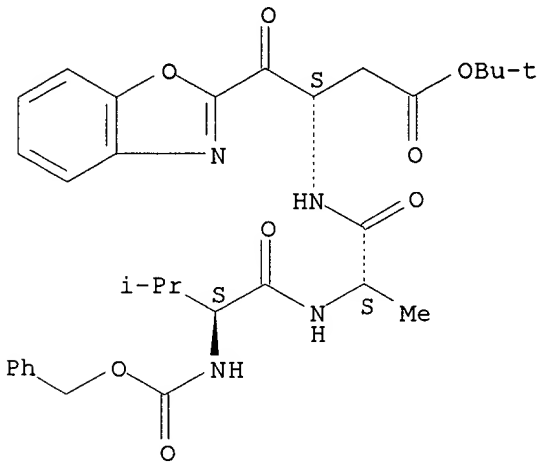


IT **175211-11-7P 175211-18-4P 175211-19-5P**
**175211-35-5P 175211-49-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(prepn. of peptide inhibitors of interleukin-1.beta. converting enzyme)

RN 175211-11-7 HCAPLUS
CN L-Alaninamide, N-[(phenylmethoxy)carbonyl]-L-valyl-N-[(1S)-1-(2-benzoxazolylcarbonyl)-3-(1,1-dimethylethoxy)-3-oxopropyl]- (9CI) (CA INDEX NAME)

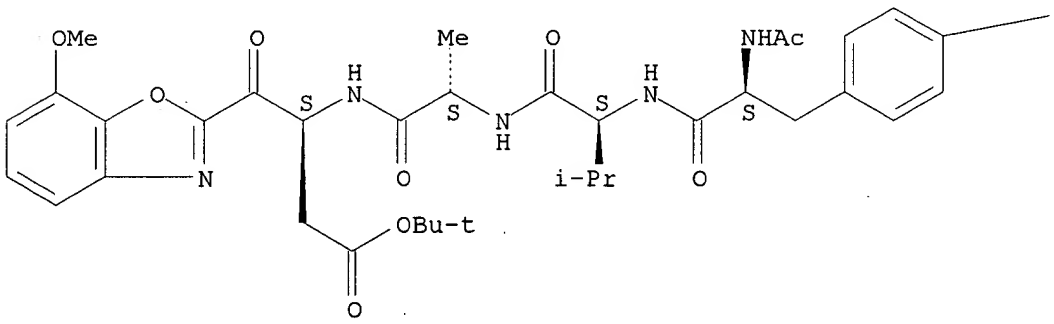
Absolute stereochemistry. Rotation (-).



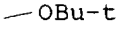
RN 175211-18-4 HCAPLUS
CN L-Alaninamide, N-acetyl-O-(1,1-dimethylethyl)-L-tyrosyl-L-valyl-N-[(1S)-3-(1,1-dimethylethoxy)-1-[(7-methoxy-2-benzoxazolyl)carbonyl]-3-oxopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



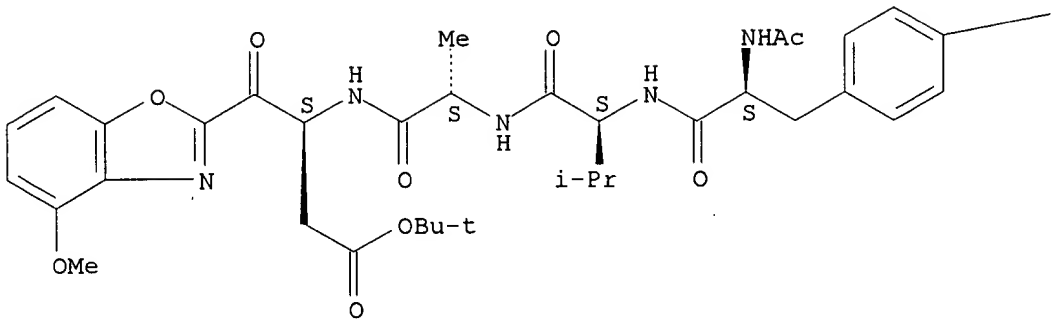
PAGE 1-B



RN 175211-19-5 HCAPLUS
CN L-Alaninamide, N-acetyl-O-(1,1-dimethylethyl)-L-tyrosyl-L-valyl-N-[(1S)-3-(1,1-dimethylethoxy)-1-[(4-methoxy-2-benzoxazolyl)carbonyl]-3-oxopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

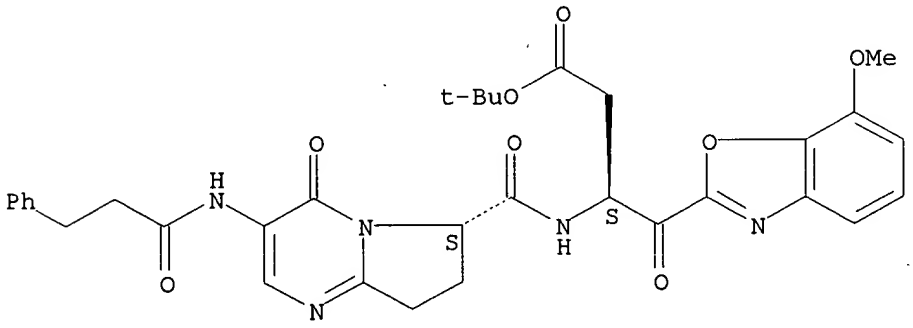



PAGE 1-B

—OBu-t

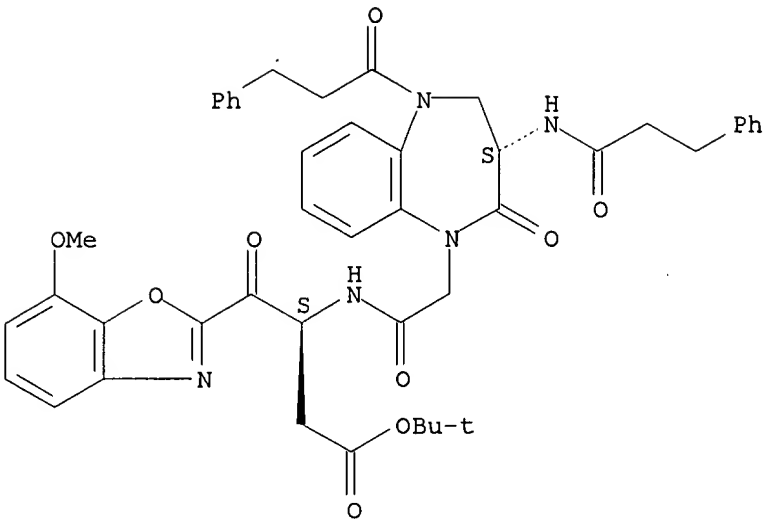
RN 175211-35-5 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[[(6S)-4,6,7,8-tetrahydro-4-oxo-3-[(1-oxo-3-phenylpropyl)amino]pyrrolo[1,2-a]pyrimidin-6-yl]carbonyl]amino]-, 1,1-dimethylethyl ester, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.




RN 175211-49-1 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[[(3S)-2,3,4,5-tetrahydro-2-oxo-5-(1-oxo-3-phenylpropyl)-3-[(1-oxo-3-phenylpropyl)amino]-1H-1,5-benzodiazepin-1-yl]acetyl]amino]-, 1,1-dimethylethyl ester, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:541852 HCAPLUS
DOCUMENT NUMBER: 127:234612
TITLE: Preparation of heterocyclyl aspartaldehyde peptide derivatives as interleukin-1.beta. converting enzyme inhibitors
INVENTOR(S): Bemis, Guy W.; Golec, Julian M. C.; Lauffer, David J.; Mullican, Michael D.; Murcko, Mark A.; Livingston, David J.
PATENT ASSIGNEE(S): Vertex Pharmaceuticals, Inc., USA
SOURCE: U.S., 67 pp., Cont.-in-part of U.S. Ser. No. 261,452. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5656627 | A | 19970812 | US 1995-405581 | 19950317 |
| US 5756466 | A | 19980526 | US 1994-261452 | 19940617 |
| US 5847135 | A | 19981208 | US 1995-440898 | 19950525 |
| US 5716929 | A | 19980210 | US 1995-464964 | 19950605 |
| US 6025147 | A | 20000215 | US 1995-460973 | 19950605 |
| ZA 9504988 | A | 19961217 | ZA 1995-4988 | 19950615 |
| CA 2192089 | AA | 19951228 | CA 1995-2192089 | 19950616 |
| WO 9535308 | A1 | 19951228 | WO 1995-US7617 | 19950616 |

W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

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| AU 9529446 | A1 | 19960115 | AU 1995-29446 | 19950616 |
| AU 709114 | B2 | 19990819 | | |
| EP 784628 | A1 | 19970723 | EP 1995-925257 | 19950616 |
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| HU 76622 | A2 | 19971028 | HU 1996-3475 | 19950616 |
| JP 10504285 | T2 | 19980428 | JP 1996-502478 | 19950616 |
| NO 9605365 | A | 19970217 | NO 1996-5365 | 19961213 |
| FI 9605036 | A | 19970214 | FI 1996-5036 | 19961216 |
| US 5973111 | A | 19991026 | US 1997-828941 | 19970328 |
| US 6420522 | B1 | 20020716 | US 1999-430822 | 19991029 |
| US 2002099042 | A1 | 20020725 | US 2001-886773 | 20010621 |

PRIORITY APPLN. INFO.: US 1994-261452 A2 19940617
US 1995-405581 A2 19950317
US 1995-440898 A3 19950525
US 1995-465216 A3 19950605
WO 1995-US7617 W 19950616
US 1999-430822 A3 19991029

OTHER SOURCE(S): MARPAT 127:234612

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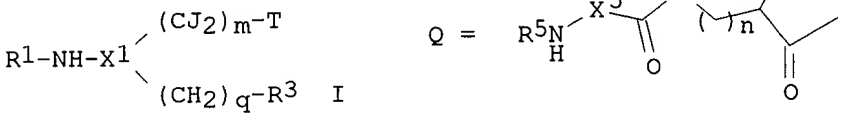

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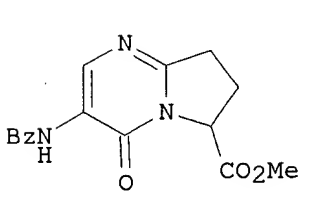

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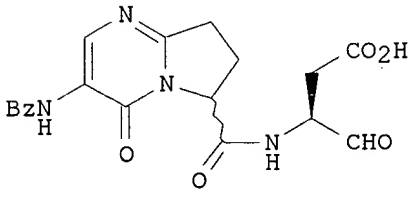


III

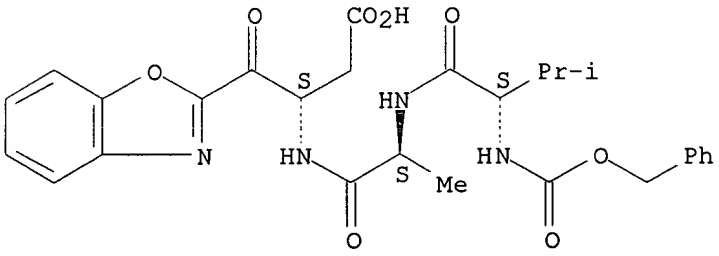
AB The present invention relates to novel classes of compds. I [X1 = CH, N; q = 0, 1; J = independently H, OH, F; m = 0-2; T = Ar3, OH, CF3, COCO2H, CO2H, COCH2OH, CONHOH, SO2NHR, SO3H, P(O)(OH)NH2, CONHCN, OSO3H, CONHSO2R16, PO3H2, P(O)(OH)OR16, P(O)(OH)R16, OPO3H2, OP(O)(OH)OR16, OP(O)(OH)R16, NHPO3H2, NHP(O)(OH)OR16, NHP(O)(OH)R16, COCH:C(OH)CO2H, 5- or 6-membered heterocyclic ring; R16 = C1-6 alkyl; R1 = optionally substituted fragment Q; X2 = O, CH2, NH, S, S(O), SO2; X5 = CH, N; n = 0-1, d = 0-2, such that n + d + d = 2; R3 = CN, CH:CHR9, CH:NOR9, (CH2)1-3T1R9, CJ2R9, COR13, COCONR5R10; each R4 = H, Ar1, R9, T1R9, (CH2)1-3T1R9; each T1 = CH:CH, O, S, S(O), SO2, NR10, NR10CO, CO, O2C, CO2, CONR10, O2CNR10, NR10CONR10, SO2NR10, NR10SO2, NR10SO2NR10; R5 = H, Ar1, COAr1, SO2Ar1, R9, CONR9, CO2R9, SO2R9, CONAr1R10, SO2NAr1R10,

CONR9R10, SO2NR9R10; R5 = Ar1, SO2Ar1, COR9, CONAr1R10, SO2NAr1R10, CONR9R10, SO2NR9R10; R9 = optionally substituted, straight or branched C1-6 alkyl; R10 = H, C1-6 straight or branched alkyl; R13 = H, Ar1, Ar2, R9, T1R9, (CH2)1-3T1R9; Ar1 = aryl, cycloalkyl, or heterocyclyl group contg. 1-3 rings and 3-15 ring atoms; Ar2 = optionally benzo-fused 5-membered heterocyclyl; Ar3 = optionally substituted Ph or 5-membered heterocyclic ring] which are inhibitors of interleukin-1.beta. converting enzyme. The ICE inhibitors of this invention are characterized by specific structural and physicochem. features. This invention also relates to pharmaceutical compns. comprising these compds. The compds. and pharmaceutical compns. of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against interleukin-1 mediated diseases, including inflammatory diseases, autoimmune diseases and neurodegenerative diseases. This invention also relates to methods for inhibiting ICE activity and methods for treating interleukin-1 mediated diseases using the compds. and compns. of this invention. Thus, cyclocondensation of Et 2-aminopyrrolidine-5-carboxylate with 4-ethoxymethylene-2-phenyl-2-oxazolidin-2-one gave 32% pyrrolopyrimidine II. Sapon. of II, followed by coupling with tert-Bu (3S)-amino-4-oxobutanoate semicarbazone, diastereomer sepn., and deprotection, gave ICE inhibitors III. III and related compds. inhibited ICE with Ki = 0.011 to 35 .mu.M in a UV-visible assay and IC50 = 0.50 to >35 .mu.M in a cell assay.

IT **175209-23-1P 192753-37-0P 192753-38-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclyl aspartaldehyde peptide derivs. as interleukin-1.beta. converting enzyme inhibitors)

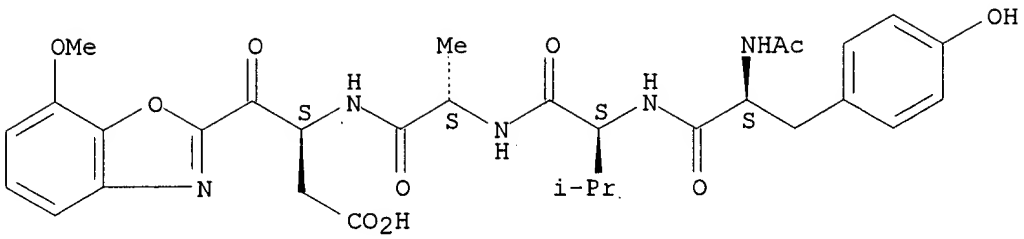
RN 175209-23-1 HCAPLUS
CN L-Alaninamide, N-[(phenylmethoxy)carbonyl]-L-valyl-N-[(1S)-2-(2-benzoxazolyl)-1-(carboxymethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



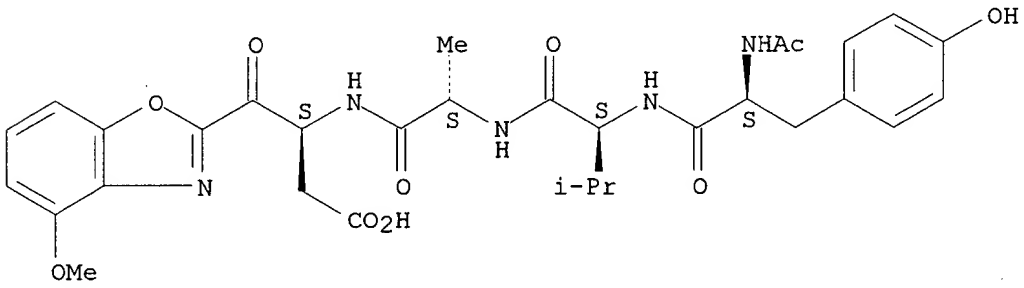

RN 192753-37-0 HCAPLUS
CN L-Alaninamide, N-acetyl-L-tyrosyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(7-methoxy-2-benzoxazolyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



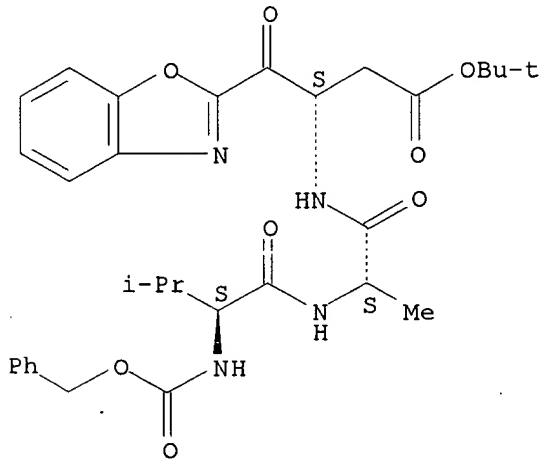
RN 192753-38-1 HCAPLUS
CN L-Alaninamide, N-acetyl-L-tyrosyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(4-methoxy-2-benzoxazolyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **175211-11-7P 175211-18-4P 175211-19-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of heterocyclyl aspartaldehyde peptide derivs. as interleukin-1.beta. converting enzyme inhibitors)
RN 175211-11-7 HCAPLUS
CN L-Alaninamide, N-[(phenylmethoxy)carbonyl]-L-valyl-N-[(1S)-1-(2-benzoxazolylcarbonyl)-3-(1,1-dimethylethoxy)-3-oxopropyl]- (9CI) (CA INDEX NAME)

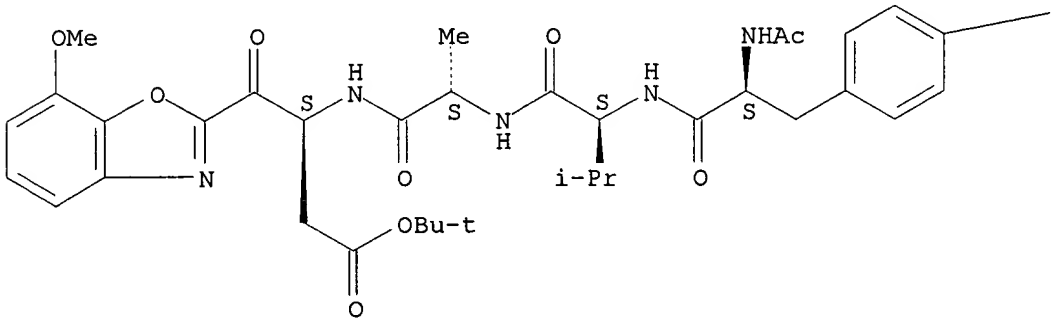
Absolute stereochemistry. Rotation (-).



RN 175211-18-4 HCAPLUS
CN L-Alaninamide, N-acetyl-O-(1,1-dimethylethyl)-L-tyrosyl-L-valyl-N-[(1S)-3-(1,1-dimethylethoxy)-1-[(7-methoxy-2-benzoxazolyl)carbonyl]-3-oxopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A




PAGE 1-B

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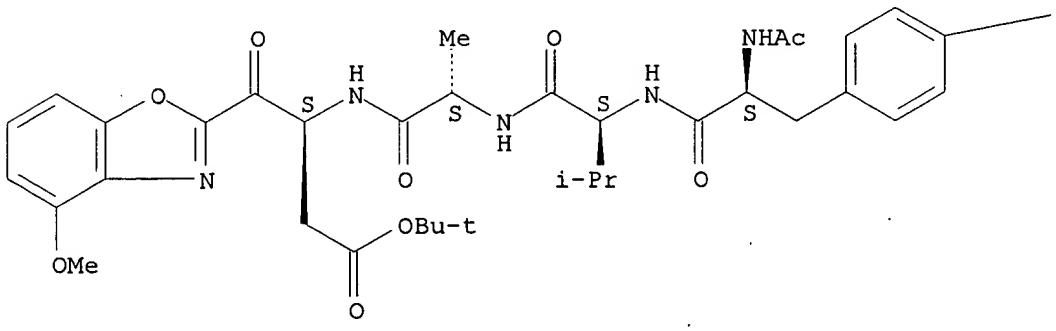
RN 175211-19-5 HCAPLUS
CN L-Alaninamide, N-acetyl-O-(1,1-dimethylethyl)-L-tyrosyl-L-valyl-N-[(1S)-3-(1,1-dimethylethoxy)-1-[(4-methoxy-2-benzoxazolyl)carbonyl]-3-oxopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A




PAGE 1-B

—OBu-t

L36 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:502830 HCAPLUS

DOCUMENT NUMBER: 127:122000
TITLE: Inhibitors of interleukin-1.beta. converting enzyme
INVENTOR(S): Batchelor, Mark J.; Bebbington, David; Bemis, Guy W.; Fridman, Wolf Herman; Gillespie, Roger J.; Golec, Julian M. C.; Gu, Yong; Lauffer, David J.; Livingston, David J.; Matharu, Saroop S.; Mullican, Michael D.; Murcko, Mark A.; Murdoch, Robert; Nyce, Philip L.; Robidoux, Andrea L. C.; et al.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 946 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9722619 | A2 | 19970626 | WO 1996-US20843 | 19961220 |
| WO 9722619 | A3 | 19971016 | | |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 6008217 | A | 19991228 | US 1995-575641 | 19951220 |
| US 5874424 | A | 19990223 | US 1996-598332 | 19960208 |
| US 5985863 | A | 19991116 | US 1996-712878 | 19960912 |
| US 6204261 | B1 | 20010320 | US 1996-761483 | 19961206 |
| AU 9715222 | A1 | 19970714 | AU 1997-15222 | 19961220 |
| AU 735075 | B2 | 20010628 | | |
| EP 869967 | A2 | 19981014 | EP 1996-945318 | 19961220 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 9612258 | A | 19990713 | BR 1996-12258 | 19961220 |
| JP 2002507961 | T2 | 20020312 | JP 1997-523098 | 19961220 |
| NO 9802597 | A | 19980812 | NO 1998-2597 | 19980605 |

PRIORITY APPLN. INFO.:
US 1995-575641 A 19951220
US 1996-598332 A 19960208
US 1996-712878 A 19960912
US 1996-31495P P 19961126
US 1996-761483 A 19961206
WO 1996-US20843 W 19961220

OTHER SOURCE(S): MARPAT 127:122000

AB Compds. R(CH2)nCH(NHR1)(CR22)mR3 [R = NC, R4CH:CH, R4ON:CH, R4CR22, etc. where R2 is independently selected from H, OH, F and R4 is (un)substituted alkyl; R1 = R5NHCHR6CONR7CHR8CO, where CHR6CONR7 is a 2-oxoazepine ring substituted by benzo, pyrido, thieno, or related rings at the 6,7-position and optionally may have O, NH, S, SO, or SO2 at the 5-position, R5 and R8 are H, cyclic group, etc.; R3 = OH, COCOCO2H, CO2H, or any bioisosteric replacement for CO2H; m = 0, 1, 2; n = 0, 1] were prepd. as inhibitors of interleukin-1.beta. converting enzyme. Thus, [1S,9S(2RS,3S)]-9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide was prepd. and shown to have IC50 values of 900 and 600 nM, resp., in the

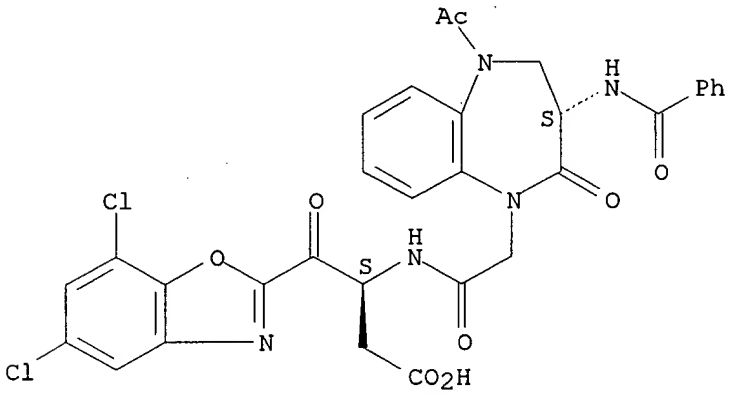
peripheral blood mononuclear cell (PBMC) and whole human blood assays.

IT **192758-50-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(inhibitors of interleukin-1.beta. converting enzyme)

RN 192758-50-2 HCAPLUS

CN 2-Benzoxazolebutanoic acid, .beta.-[[[(3S)-5-acetyl-3-(benzoylamino)-2,3,4,5-tetrahydro-2-oxo-1H-1,5-benzodiazepin-1-yl]acetyl]amino]-5,7-dichloro-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

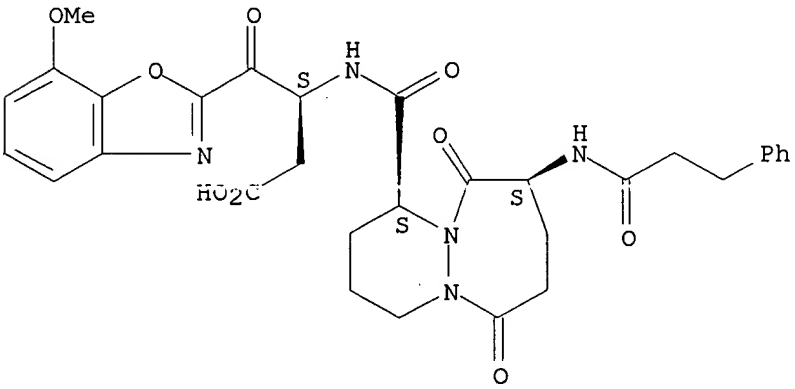



IT **175209-35-5P 175209-36-6P 175209-84-4P**
**192754-56-6P 192754-57-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibitors of interleukin-1.beta. converting enzyme)

RN 175209-35-5 HCAPLUS

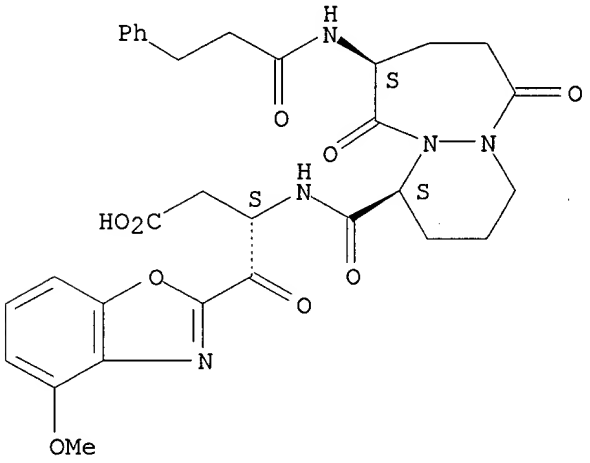
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.beta.-[[[(1S,9S)-octahydro-6,10-dioxo-9-[(1-oxo-3-phenylpropyl)amino]-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



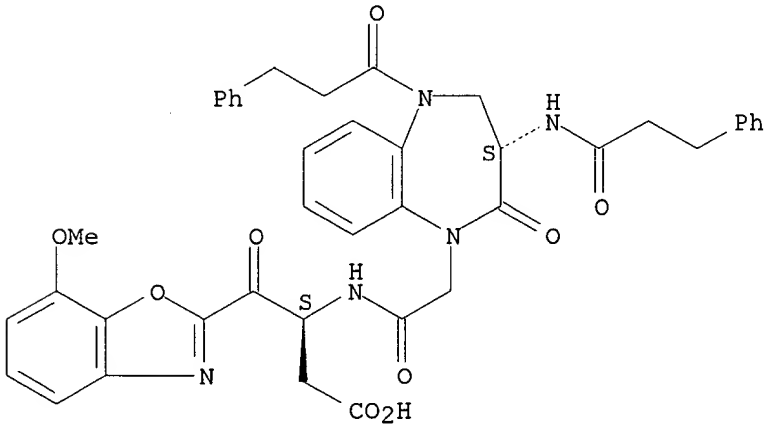
RN 175209-36-6 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 4-methoxy-.beta.-[[[(1S,9S)-octahydro-6,10-dioxo-9-[(1-oxo-3-phenylpropyl)amino]-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



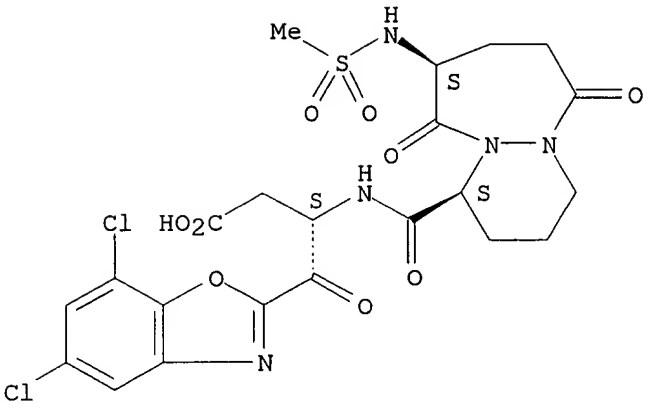
RN 175209-84-4 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[[(3S)-2,3,4,5-tetrahydro-2-oxo-5-(1-oxo-3-phenylpropyl)-3-[(1-oxo-3-phenylpropyl)amino]-1H-1,5-benzodiazepin-1-yl]acetyl]amino]-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



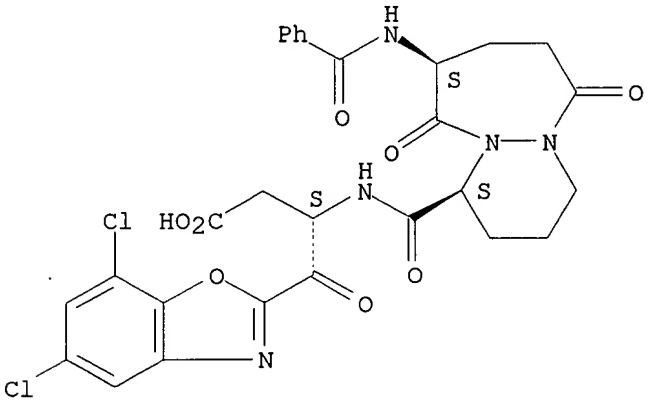
RN 192754-56-6 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 5,7-dichloro-.beta.-[[[(1S,9S)-octahydro-9-[(methylsulfonyl)amino]-6,10-dioxo-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 192754-57-7 HCAPLUS
CN 2-Benzoxazolebutanoic acid, .beta.-[[[(1S,9S)-9-(benzoylamino)octahydro-6,10-dioxo-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-5,7-dichloro-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **175211-18-4P 175211-19-5P 192753-85-8P**
**192755-85-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of interleukin-1.beta. converting enzyme)
RN 175211-18-4 HCAPLUS
CN L-Alaninamide, N-acetyl-O-(1,1-dimethylethyl)-L-tyrosyl-L-valyl-N-[(1S)-3-(1,1-dimethylethoxy)-1-[(7-methoxy-2-benzoxazolyl)carbonyl]-3-oxopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

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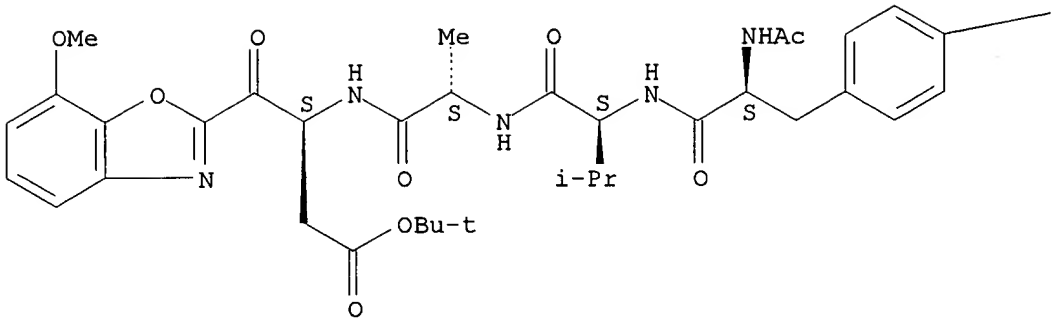

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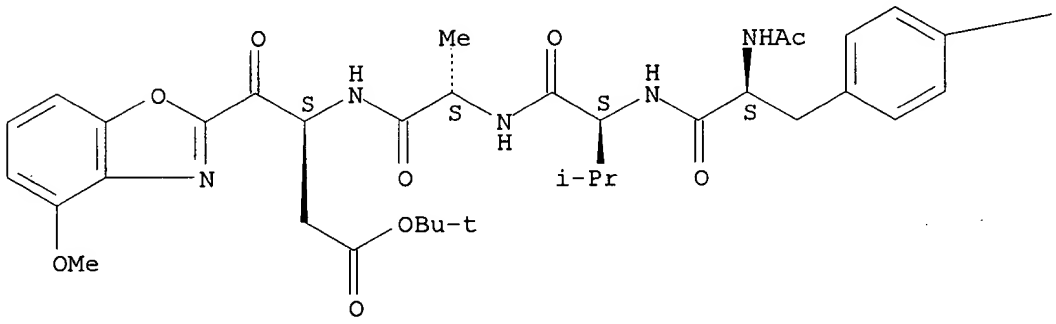
RN 175211-19-5 HCAPLUS
CN L-Alaninamide, N-acetyl-O-(1,1-dimethylethyl)-L-tyrosyl-L-valyl-N-[(1S)-3-(1,1-dimethylethoxy)-1-[(4-methoxy-2-benzoxazolyl)carbonyl]-3-oxopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

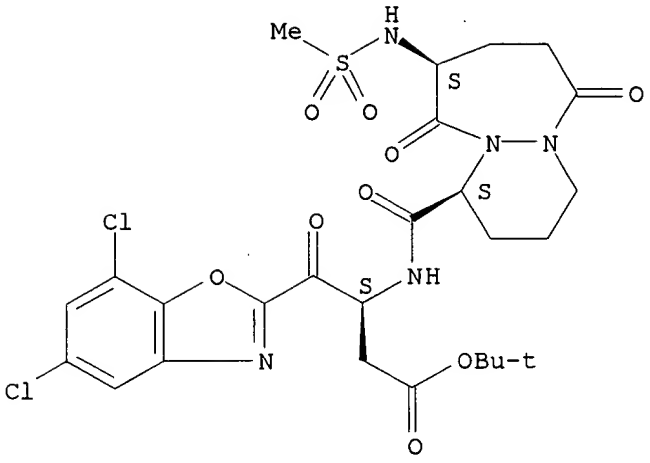


PAGE 1-B

—OBu-t

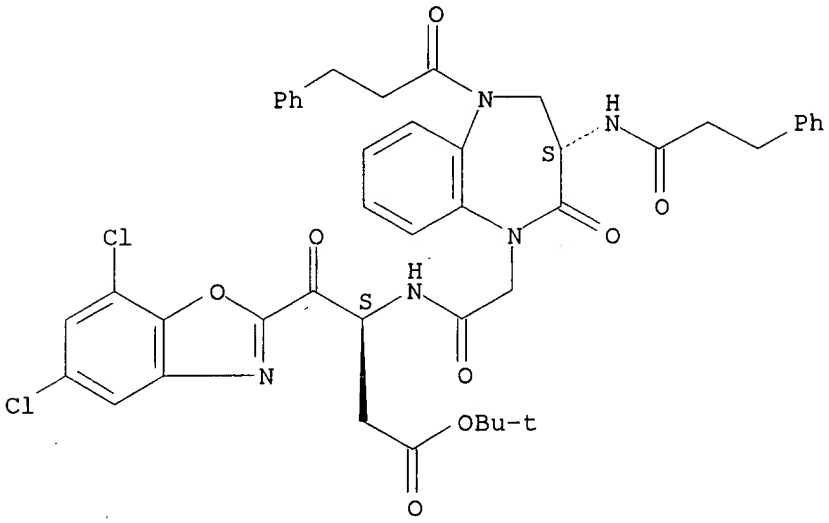
RN 192753-85-8 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 5,7-dichloro-.beta.-[[[(1S,9S)-octahydro-9-[(methylsulfonyl)amino]-6,10-dioxo-6H pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-.gamma.-oxo-, 1,1-dimethylethyl ester, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



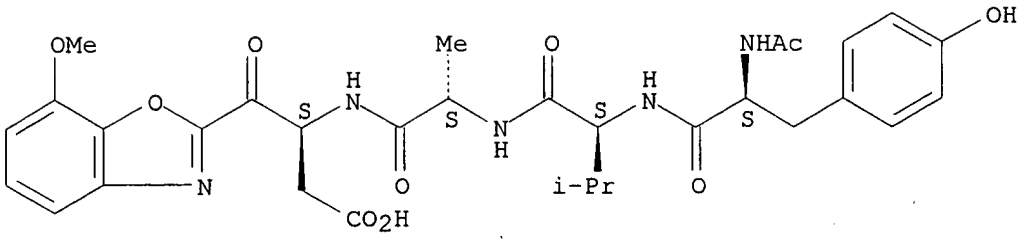
RN 192755-85-4 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 5,7-dichloro-.gamma.-oxo-.beta.-[[[(3S)-2,3,4,5-tetrahydro-2-oxo-5-(1-oxo-3-phenylpropyl)-3-[(1-oxo-3-phenylpropyl)amino]-1H-1,5-benzodiazepin-1-yl]acetyl]amino]-, 1,1-dimethylethyl ester, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



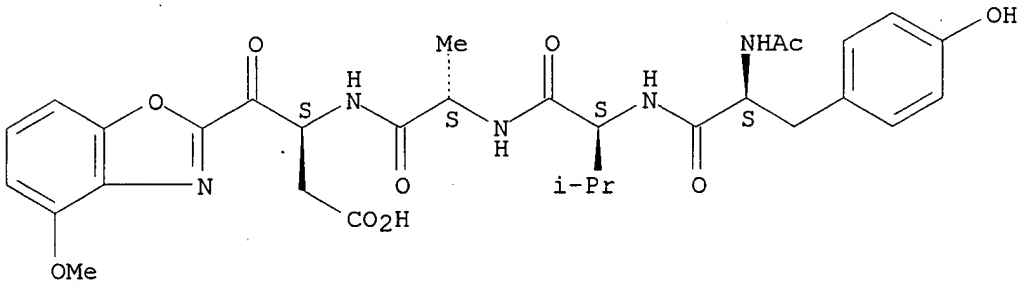
IT **192753-37-0P 192753-38-1P 192753-87-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(inhibitors of interleukin-1.beta. converting enzyme)
RN 192753-37-0 HCAPLUS
CN L-Alaninamide, N-acetyl-L-tyrosyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(7-methoxy-2-benzoxazolyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



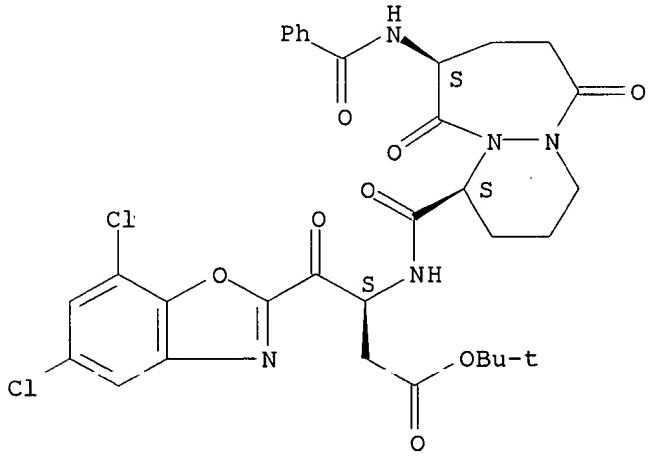
RN 192753-38-1 HCAPLUS
CN L-Alaninamide, N-acetyl-L-tyrosyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(4-methoxy-2-benzoxazolyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 192753-87-0 HCAPLUS
CN 2-Benzoxazolebutanoic acid, .beta.-[[[(1S,9S)-9-(benzoylamino)octahydro-6,10-dioxo-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-5,7-dichloro-.gamma.-oxo-, 1,1-dimethylethyl ester, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



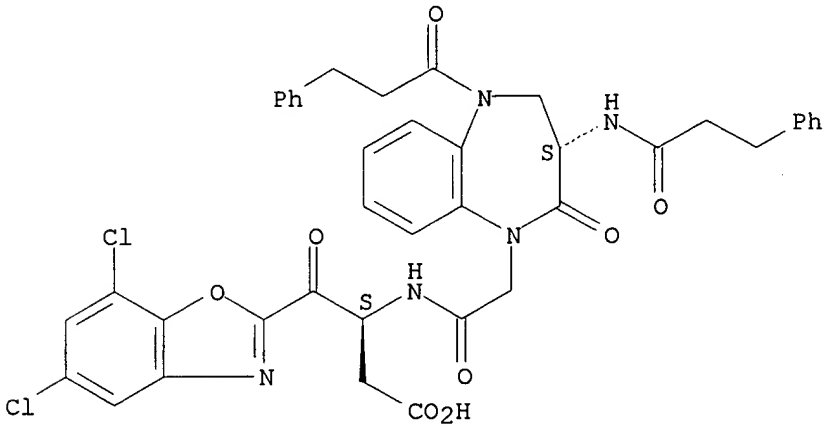
IT **192758-04-6P 192758-74-0P 192760-11-5P 192760-12-6P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological

study); PREP (Preparation); USES (Uses)
(inhibitors of interleukin-1.beta. converting enzyme)

RN 192758-04-6 HCAPLUS

CN 2-Benzoxazolebutanoic acid, 5,7-dichloro-.gamma.-oxo-.beta.-[[[(3S)-2,3,4,5-tetrahydro-2-oxo-5-(1-oxo-3-phenylpropyl)-3-[(1-oxo-3-phenylpropyl)amino]-1H-1,5-benzodiazepin-1-yl]acetyl]amino]-, (.beta.S)-(9CI) (CA INDEX NAME)

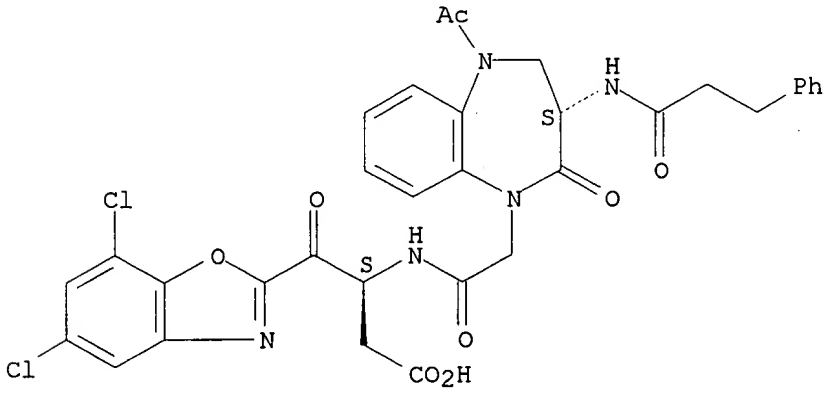
Absolute stereochemistry.



RN 192758-74-0 HCAPLUS

CN 2-Benzoxazolebutanoic acid, .beta.-[[[5-acetyl-2,3,4,5-tetrahydro-2-oxo-3-[(1-oxo-3-phenylpropyl)amino]-1H-1,5-benzodiazepin-1-yl]acetyl]amino]-5,7-dichloro-.gamma.-oxo-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

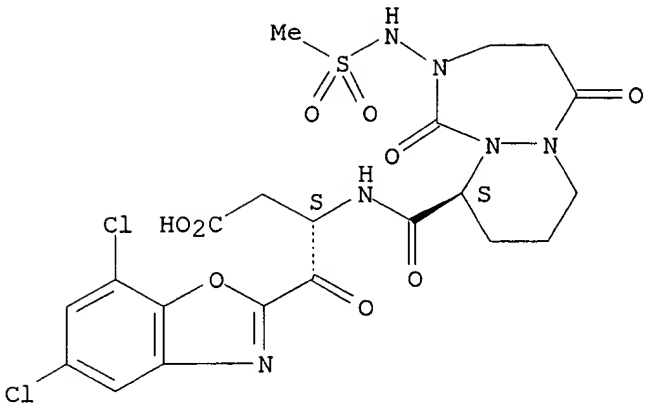
Absolute stereochemistry.



RN 192760-11-5 HCAPLUS

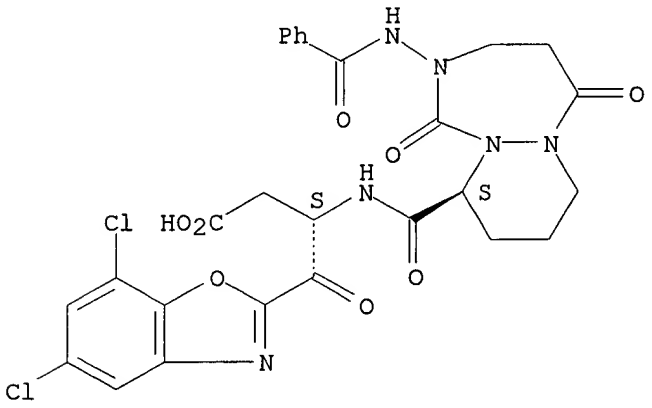
CN 2-Benzoxazolebutanoic acid, 5,7-dichloro-.beta.-[[[octahydro-2-[(methylsulfonyl)amino]-1,5-dioxo-1H-pyridazino[1,2-a][1,2,4]triazepin-10-yl]carbonyl]amino]-.gamma.-oxo-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 192760-12-6 HCAPLUS
CN 2-Benzoxazolebutanoic acid, .beta.-[[[2-(benzoylamino)octahydro-1,5-dioxo-1H-pyridazino[1,2-a][1,2,4]triazepin-10-yl]carbonyl]amino]-5,7-dichloro-.gamma.-oxo-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L36 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:501329 HCAPLUS
DOCUMENT NUMBER: 127:109198
TITLE: Inhibitors of interleukin-1.beta. converting enzyme
INVENTOR(S): Bemis, Guy W.; Duffy, John P.; Fridman, Wolf Herman; Golec, Julian M. C.; Livingston, David J.; Mullican, Michael D.; Murcko, Mark A.; Zelle, Robert E.
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

WO 9722618 A1 19970626 WO 1996-US20370 19961220
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
US 5843904 A 19981201 US 1995-575648 19951220
CA 2240489 AA 19970626 CA 1996-2240489 19961220
ZA 9610797 A 19970626 ZA 1996-10797 19961220
AU 9714658 A1 19970714 AU 1997-14658 19961220
AU 722936 B2 20000817
EP 876395 A1 19981111 EP 1996-945237 19961220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO
CN 1207743 A 19990210 CN 1996-199733 19961220
BR 9612191 A 19990713 BR 1996-12191 19961220
JP 2000503635 T2 20000328 JP 1997-523008 19961220
US 6162790 A 20001219 US 1998-24537 19980217
NO 9802774 A 19980819 NO 1998-2774 19980616
PRIORITY APPLN. INFO.: US 1995-575648 A 19951220
WO 1996-US20370 W 19961220
OTHER SOURCE(S): MARPAT 127:109198

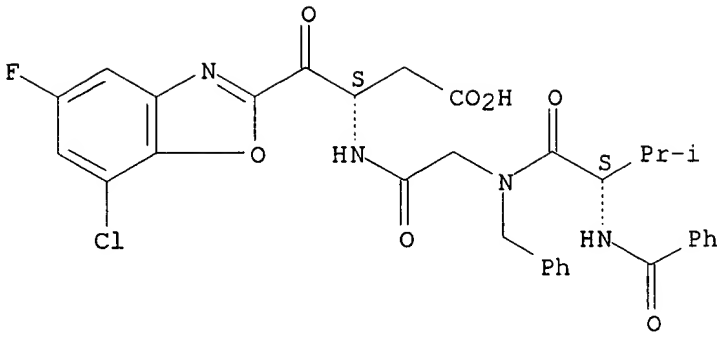
AB Compds. R5(NHCHR4CO)nNR3CH2CONHCH[CH(OR2)(OR1)](CH2)mCO2R [R = H, (un)substituted alkyl; R1, R2 = R6, COR6, CONHR6 (R6 = aryl, alkyl, aralkyl, etc.); R1 and R2 may form a satd. cyclic group; or corresponding anhydrides for the case of R = R1 = H; R3 = arylmethyl, non-arom. cyclic group; R4 = (un)substituted alkyl; R5 = COR6, CO2H or ester or amide derivs., SO2R6, COCOR6, R6, H; m = 1, 2; n = 0-2] were prepd. as inhibitors of interleukin-1.beta. converting enzyme (ICE). Thus, (S)-Bz-L-Val-N(Bzl)CH2CONHCH(CH2CO2CO2H)CHO was prepd. via peptide coupling in soln. and found to have an ICE inhibition const. (Ki) of 69 nM.

IT **192583-04-3P 192583-05-4P 192583-09-8P 192583-10-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibitors of interleukin-1.beta. converting enzyme)

RN 192583-04-3 HCAPLUS

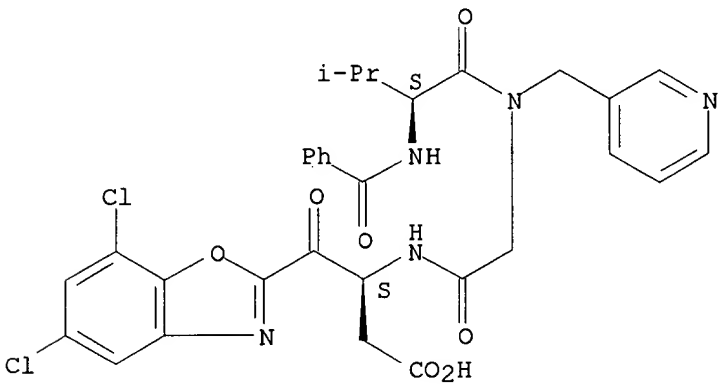
CN Glycinamide, N-benzoyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(7-chloro-5-fluoro-2-benzoxazolyl)-2-oxoethyl]-N2-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



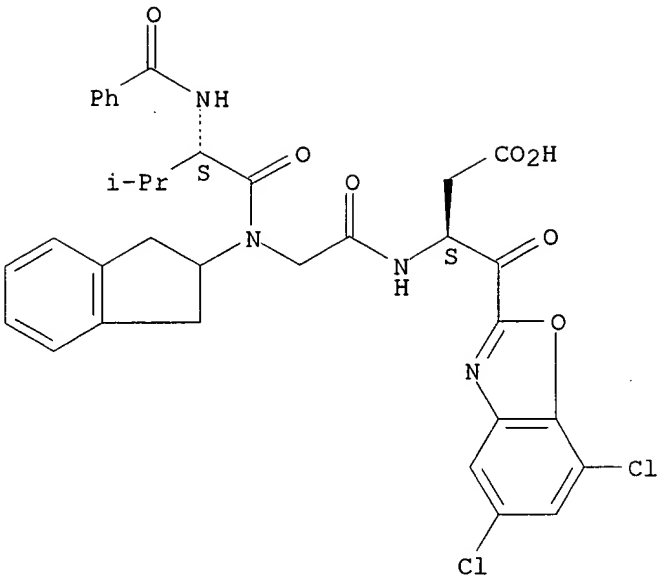
RN 192583-05-4 HCAPLUS
CN Glycinamide, N-benzoyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(5,7-dichloro-2-benzoxazolyl)-2-oxoethyl]-N2-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



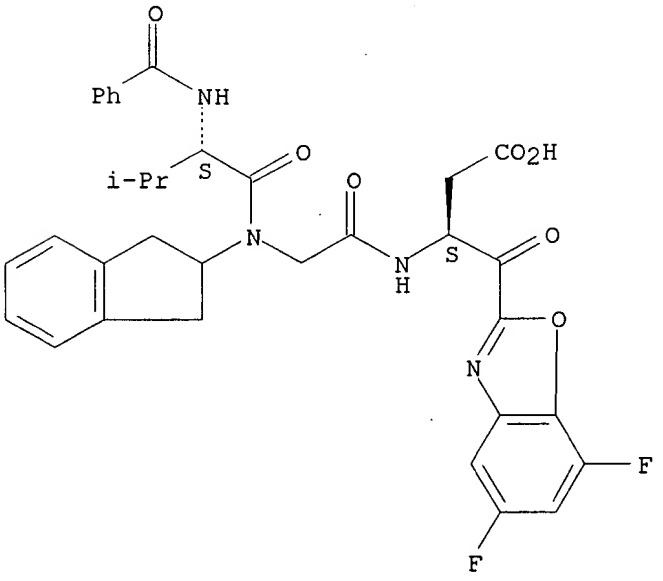
RN 192583-09-8 HCAPLUS
CN Glycinamide, N-benzoyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(5,7-dichloro-2-benzoxazolyl)-2-oxoethyl]-N2-(2,3-dihydro-1H-inden-2-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 192583-10-1 HCAPLUS
CN Glycinamide, N-benzoyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(5,7-difluoro-2-benzoxazolyl)-2-oxoethyl]-N2-(2,3-dihydro-1H-inden-2-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L36 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:214750 HCAPLUS
DOCUMENT NUMBER: 124:290273
TITLE: Preparation of peptide analogs as inhibitors of interleukin-1 beta converting enzyme (ICE)

INVENTOR(S): Bemis, Guy W.; Golec, Julian M. C.; Lauffer, David J.; Mullican, Michael D.; Murcko, Mark A.; Livingston, David J.
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorp., USA
SOURCE: PCT Int. Appl., 374 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9535308 | A1 | 19951228 | WO 1995-US7617 | 19950616 |
| W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT | | | | |
| RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5756466 | A | 19980526 | US 1994-261452 | 19940617 |
| US 5656627 | A | 19970812 | US 1995-405581 | 19950317 |
| US 5847135 | A | 19981208 | US 1995-440898 | 19950525 |
| AU 9529446 | A1 | 19960115 | AU 1995-29446 | 19950616 |
| AU 709114 | B2 | 19990819 | | |
| EP 784628 | A1 | 19970723 | EP 1995-925257 | 19950616 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| BR 9508051 | A | 19971021 | BR 1995-8051 | 19950616 |
| JP 10504285 | T2 | 19980428 | JP 1996-502478 | 19950616 |
| NO 9605365 | A | 19970217 | NO 1996-5365 | 19961213 |
| FI 9605036 | A | 19970214 | FI 1996-5036 | 19961216 |
| US 6420522 | B1 | 20020716 | US 1999-430822 | 19991029 |

PRIORITY APPLN. INFO.:
US 1994-261452 A 19940617
US 1995-405581 A 19950317
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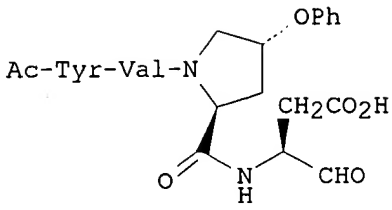
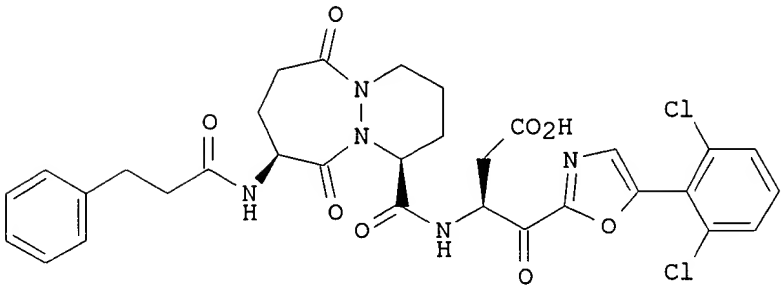
US 1995-465216 A3 19950605
WO 1995-US7617 W 19950616

OTHER SOURCE(S): MARPAT 124:290273
GI




I




II

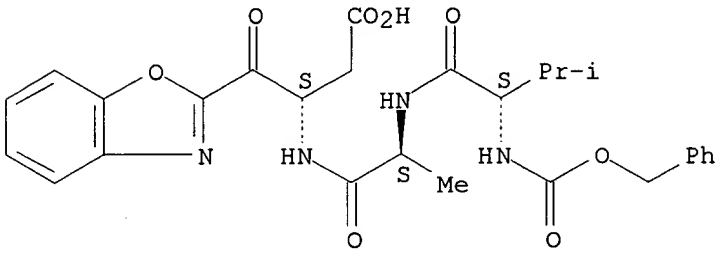
AB Novel classes of compds. are prepd., which are characterized by specific structural and physicochem. features comprising (a) a first and a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE selected from the carbonyl O and the amide NH group of Arg-341 Ser-339, (b) a first and a second moderately hydrophobic moiety, said moieties each being capable of assocg. with a sep. binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected form the P2, P3, P4, and P' binding pockets, and (c) an electroneg. moiety comprising .gtoreq.1 electroneg. atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being capable of forming .gtoreq.1 hydrogen bonds or salts bridges with residues in the P1 binding pocket of ICE. These compds. and pharmaceutical compns. of this invention are particularly well suited for inhibiting ICE activity and consequently may be advantageously used as agents against interleukin-1 mediated diseases, including inflammatory diseases, autoimmune diseases and neurodegenerative diseases. Thus, etherification of Me N-tert-butoxycarbonyl-cis-4-hydroxyprolinate with phenol using Ph3P and di-Et azodicarboxylate in THF to Me N-tert-butoxycarbonyl-cis-4-phenoxyprolinate followed by deprotection with HCl in EtOAc to Me 4-phenoxyprolinate hydrochloride and condensation with Ac-Tyr-Val-OH using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HOBT, and diisopropylethylamine in DMF gave Me N-acetyl-L-tyrosinyl-L-valyl-(4-phenoxy)prolinate. Sapon. of the latter peptide ester with LiOH in aq. THF to N-acetyl-L-tyrosinyl-L-valyl-(phenoxy)proline followed by condensation with N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran gave N-[N-acetyl-L-tyrosinyl-L-valyl-(4-phenoxy)prolinyl]-4-amino-5-benzyloxy-2-oxotetrahydrofuran (1:1 diastereomer mixt.), which underwent hydrogenolysis over Pd(OH)2 in MeOH under H atm. to give the title compd. (I). In a IL-1.beta. assay with a mixed population of human peripheral blood mononuclear cells or enriched adherent mononuclear cells, I in vitro showed IC50 of 2.6 and 0.25 .mu.M for inhibiting the processing of pre-IL-1.beta. by ICE.

IT **175209-23-1P 175209-25-3P 175209-26-4P**
**175209-31-1P 175209-32-2P 175209-35-5P**
**175209-36-6P 175209-50-4P 175209-69-5P**

**175209-70-8P 175209-78-6P 175209-84-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of peptide analogs as inhibitors of interleukin-1 beta converting enzyme for treating inflammatory, autoimmune and neurodegenerative diseases)

RN 175209-23-1 HCAPLUS
CN L-Alaninamide, N-[(phenylmethoxy)carbonyl]-L-valyl-N-[(1S)-2-(2-benzoxazolyl)-1-(carboxymethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

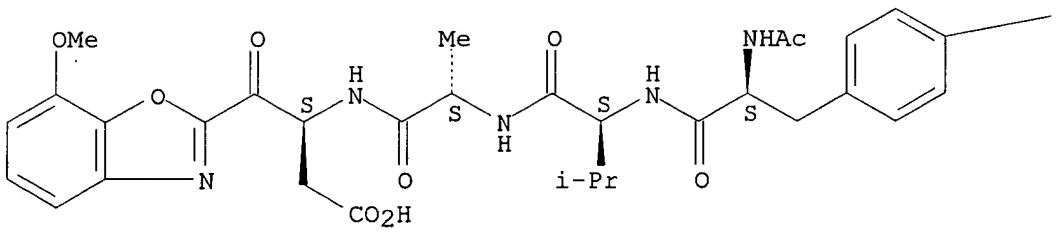
Absolute stereochemistry. Rotation (-).



RN 175209-25-3 HCAPLUS
CN L-Alaninamide, N-acetyl-O-(1,1-dimethylethyl)-L-tyrosyl-L-valyl-N-[1-(carboxymethyl)-2-(7-methoxy-2-benzoxazolyl)-2-oxoethyl]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



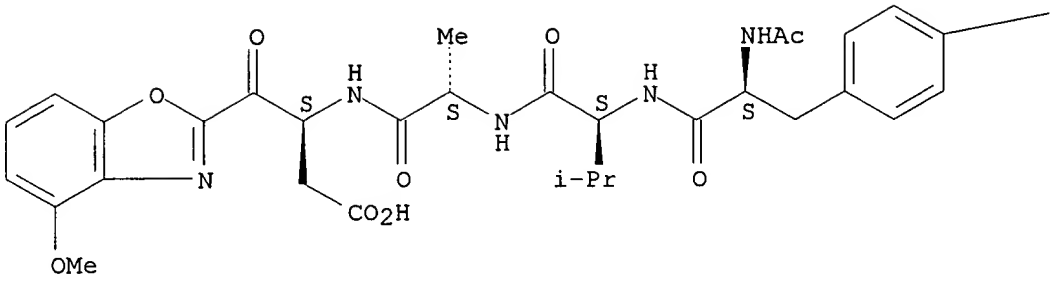
PAGE 1-B

—OBu-t

RN 175209-26-4 HCAPLUS
CN L-Alaninamide, N-acetyl-O-(1,1-dimethylethyl)-L-tyrosyl-L-valyl-N-[1-(carboxymethyl)-2-(4-methoxy-2-benzoxazolyl)-2-oxoethyl]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

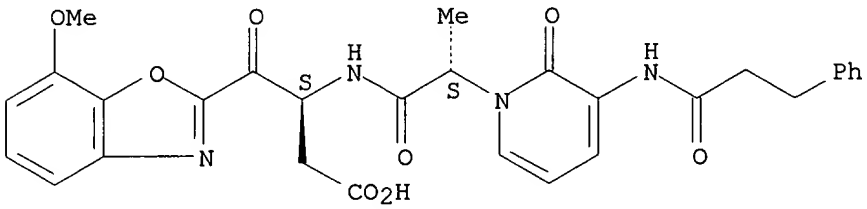


PAGE 1-B

—OBu-t

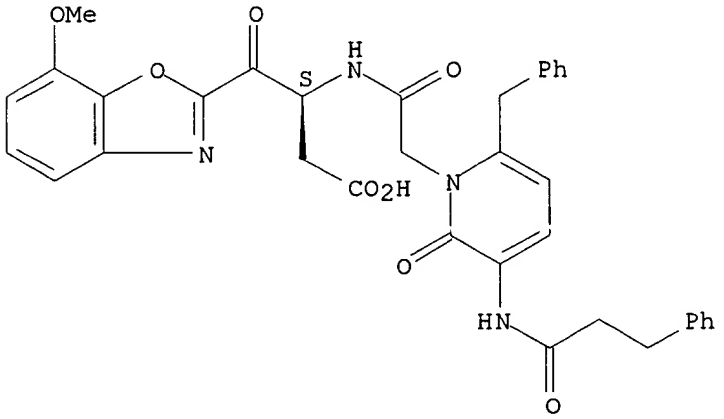
RN 175209-31-1 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[(2S)-1-oxo-2-[2-oxo-3-[(1-oxo-3-phenylpropyl)amino]-1(2H)-pyridinyl]propyl]amino]-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



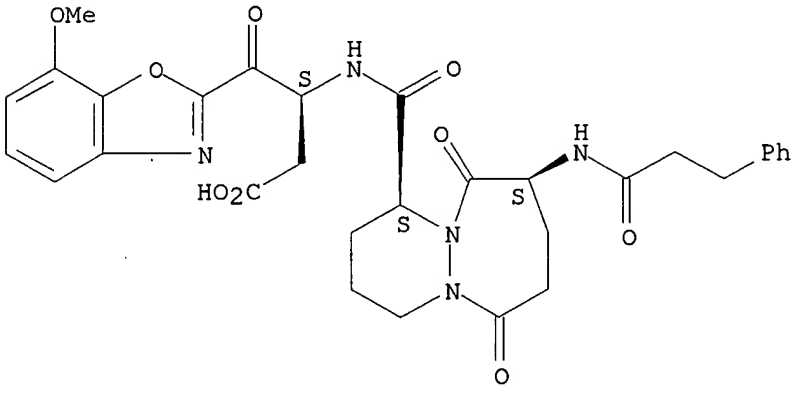
RN 175209-32-2 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[[2-oxo-3-[(1-oxo-3-phenylpropyl)amino]-6-(phenylmethyl)-1(2H)-pyridinyl]acetyl]amino]-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



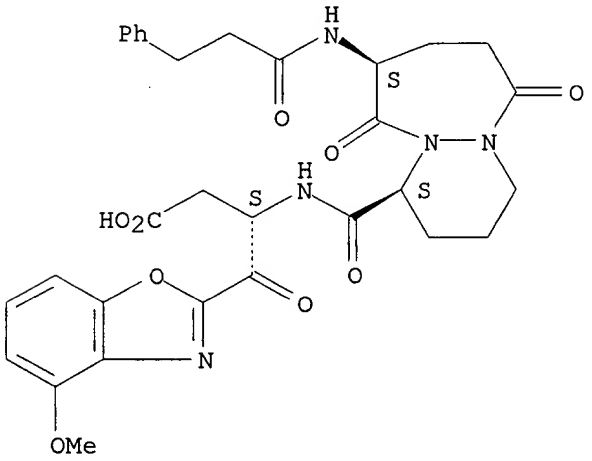
RN 175209-35-5 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.beta.-[[[(1S,9S)-octahydro-6,10-dioxo-9-[(1-oxo-3-phenylpropyl)amino]-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



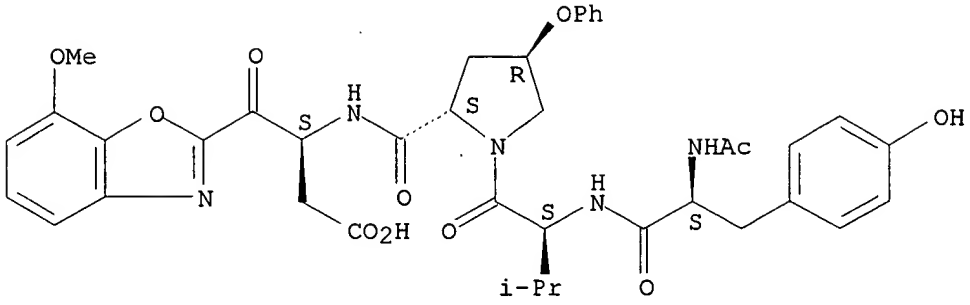
RN 175209-36-6 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 4-methoxy-.beta.-[[[(1S,9S)-octahydro-6,10-dioxo-9-[(1-oxo-3-phenylpropyl)amino]-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]carbonyl]amino]-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



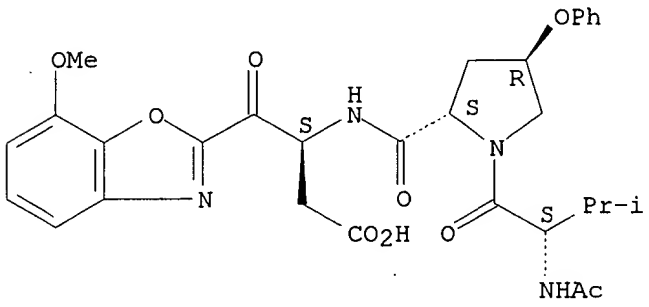
RN 175209-50-4 HCAPLUS
CN L-Prolinamide, N-acetyl-L-tyrosyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(7-methoxy-2-benzoxazolyl)-2-oxoethyl]-4-phenoxy-, (4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



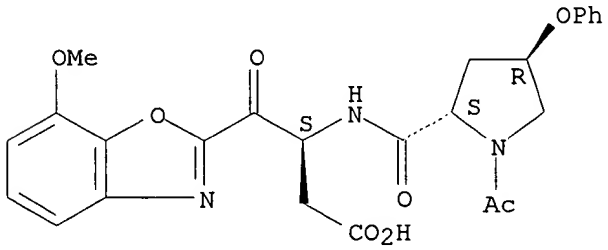
RN 175209-69-5 HCAPLUS
CN L-Prolinamide, N-acetyl-L-valyl-N-[(1S)-1-(carboxymethyl)-2-(7-methoxy-2-benzoxazolyl)-2-oxoethyl]-4-phenoxy-, (4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



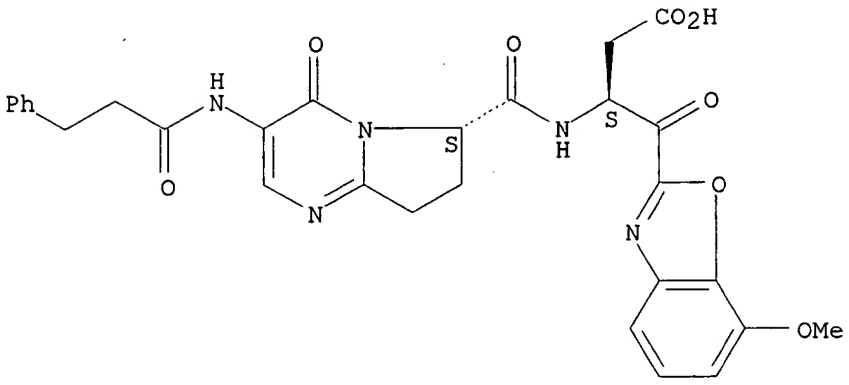
RN 175209-70-8 HCAPLUS
CN 2-Benzoxazolebutanoic acid, .beta.-[[[(2S,4R)-1-acetyl-4-phenoxy-2-pyrrolidinyl]carbonyl]amino]-7-methoxy-.gamma.-oxo-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



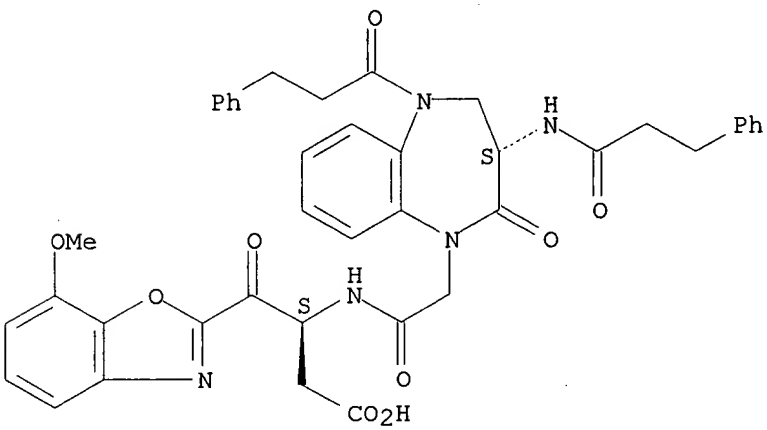
RN 175209-78-6 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[[(6S)-4,6,7,8-tetrahydro-4-oxo-3-[(1-oxo-3-phenylpropyl)amino]pyrrolo[1,2-a]pyrimidin-6-yl]carbonyl]amino]-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



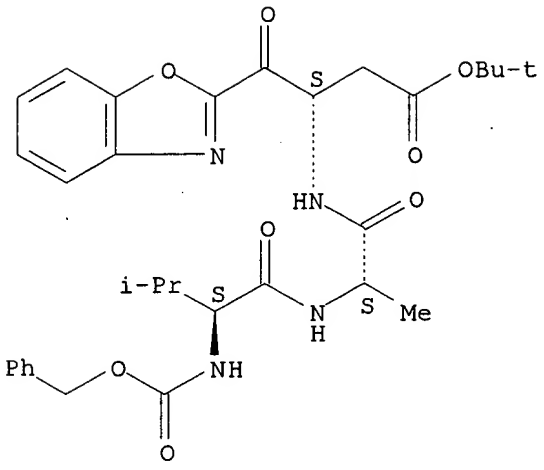
RN 175209-84-4 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[[(3S)-2,3,4,5-tetrahydro-2-oxo-5-(1-oxo-3-phenylpropyl)-3-[(1-oxo-3-phenylpropyl)amino]-1H-1,5-benzodiazepin-1-yl]acetyl]amino]-, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **175211-11-7P 175211-18-4P 175211-19-5P**
**175211-35-5P 175211-49-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of peptide analogs as inhibitors of interleukin-1 beta converting enzyme for treating inflammatory, autoimmune and neurodegenerative diseases)
RN 175211-11-7 HCAPLUS
CN L-Alaninamide, N-[(phenylmethoxy)carbonyl]-L-valyl-N-[(1S)-1-(2-benzoxazolylcarbonyl)-3-(1,1-dimethylethoxy)-3-oxopropyl]- (9CI) (CA INDEX NAME)

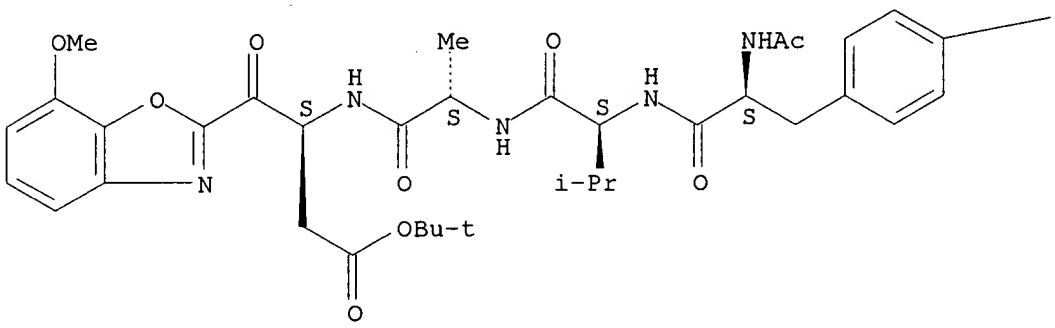
Absolute stereochemistry. Rotation (-).



RN 175211-18-4 HCAPLUS
CN L-Alaninamide, N-acetyl-O-(1,1-dimethylethyl)-L-tyrosyl-L-valyl-N-[(1S)-3-(1,1-dimethylethoxy)-1-[(7-methoxy-2-benzoxazolyl)carbonyl]-3-oxopropyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 1-B

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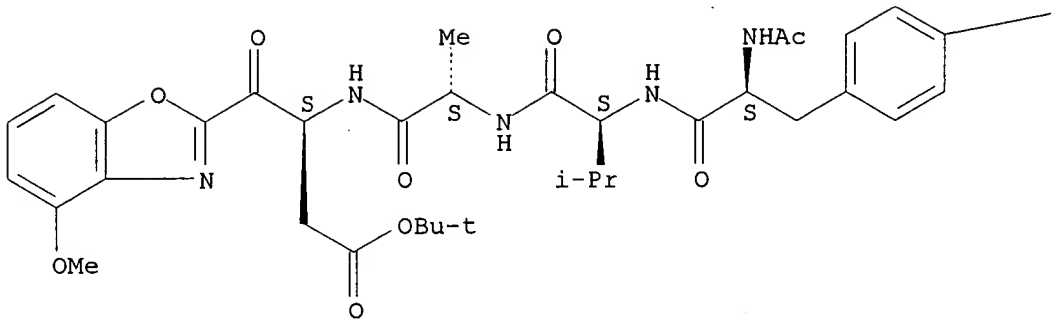
RN 175211-19-5 HCAPLUS
CN L-Alaninamide, N-acetyl-O-(1,1-dimethylethyl)-L-tyrosyl-L-valyl-N-[(1S)-3-(1,1-dimethylethoxy)-1-[(4-methoxy-2-benzoxazolyl)carbonyl]-3-oxopropyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 1-B

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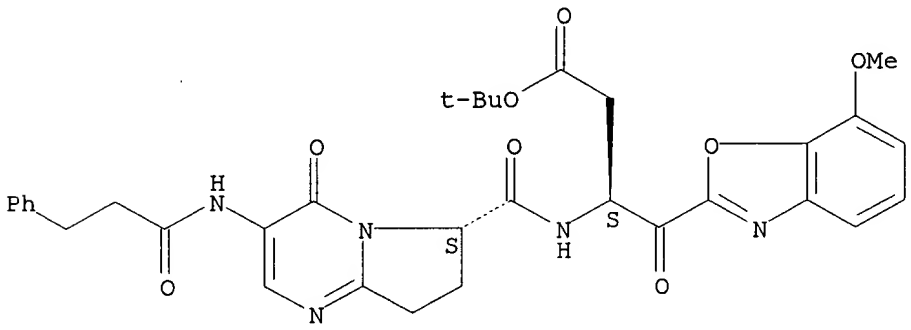
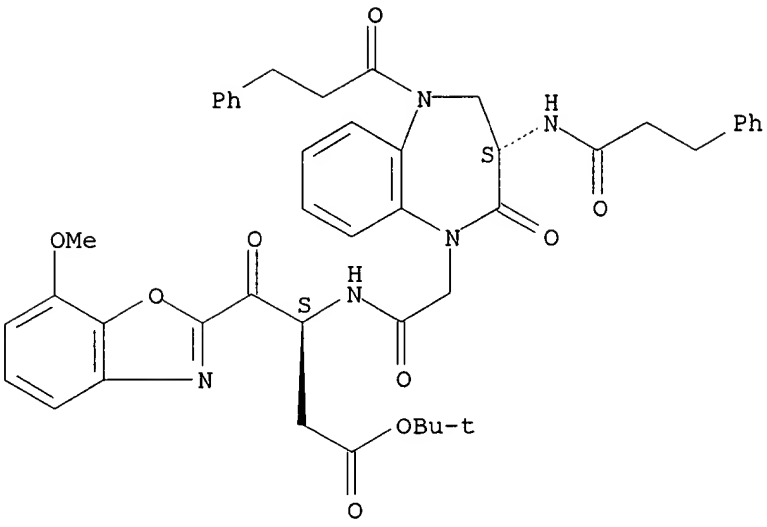
RN 175211-35-5 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[[(6S)-4,6,7,8-tetrahydro-4-oxo-3-[(1-oxo-3-phenylpropyl)amino]pyrrolo[1,2-a]pyrimidin-6-yl]carbonyl]amino]-, 1,1-dimethylethyl ester, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 175211-49-1 HCAPLUS
CN 2-Benzoxazolebutanoic acid, 7-methoxy-.gamma.-oxo-.beta.-[[[(3S)-2,3,4,5-tetrahydro-2-oxo-5-(1-oxo-3-phenylpropyl)-3-[(1-oxo-3-phenylpropyl)amino]-1H-1,5-benzodiazepin-1-yl]acetyl]amino]-, 1,1-dimethylethyl ester, (.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.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